SPECIFICATION

Tablet and Tablet Production Method

Technical Field

The present invention relates to a tablet and a tablet production method, particularly to a tablet which is rapidly disintegrated in oral cavity and to a production method of such tablet.

Background Art

Several kinds of tablets have been used in medical and clinical field in these days. However, a tablet considering compliance of patient for dosing is a little and a tablet which is easy to be dosed for elderly person and children who have difficulty to swallow has been required to be developed.

An intrabuccally rapidly disintegrable tablet is characterized by being disintegrated rapidly in oral cavity and has an advantage of having dosing compliance such that elderly person or children who have difficulty to swallow can take without water, so that such tablet has come to the fore.

In the past such an intrabuccally rapidly disintegrable tablet was produced by adjusting moistening mass including an active substance by means of ethanol and/or water and by drying it after pouring into a mold (Refer to JP-A-2-32014).

JP-A-5-271054 discloses that a powdered mixture including an active substance, a saccharide, and water of proper degree for wetting the particle surface of a saccharide is tabletted and produced to be a tablet after drying.

The publication of WO95/20380 discloses that a saccharide such as maltose is used as a binder and a granulated material comprising at least a principal agent and a saccharide with low moldability such as lactose is compressed to produce a tablet.

However according to the production method of an intrabuccally rapidly disintegrable tablet described in JP-A-2-32014, particular method different from a regular tablet production method is used, wherein moistening mass is adjusted and dried after pouring into a mold, so that there is a problem of low productivity.

Also according to the production method of an intrabuccally rapidly disintegrable tablet described in JP-A-5-271054, particular method different from a regular tablet production

method is used, wherein a powdered mixture including medicinal properties, a saccharide, and water of proper degree for wetting the particle surface of a saccharide is tabletted and produced to be a tablet after drying, so that there is a problem of low productivity.

Further according to the tablet produced by such an intrabuccally rapidly disintegrable tablet production method, because particles are bound by a saccharide therebetween, there is a problem that binding between particles is weak and a tablet easily gets chipped while storage and transportation.

According to the oral dissolving type compressed molded material disclosed in WO95/20380, it is rapidly disintegrated in oral cavity, however, moldability of tabletting isn't enough and tabletting of such material is difficult. And in such oral dissolving type compressed molded material there is a problem that binding between particles is weak and tablet easily gets chipped while storage and transportation because particles are bound by saccharide therebetween like the tablet produced by the intrabuccally rapidly disintegrable tablet production method described in JP-A-5-271054.

Disclosure of the Invention

The present invention has been proposed to solve the above-mentioned problems. The object of the invention is to provide a tablet which is superior in disintegration and moldability in case of tabletting, has adequate hardness after compression, has superior characteristic of hardly causing chip of a tablet in case of storage and transportation, and can be produced by the same production method as an usual tablet, and to provide its production method.

The present invention relates to the following (1) - (12).

(1) The present invention relates to a tablet obtainable by binding a mixture of a principal agent, a saccharide with high wettability against water, and a disintegrant with a binder including a saccharide with high wettability against water and by compressing the granulated material.

Here the term "principal agent" used in the present invention generally means basis in a tablet having medicinal virtues expected by prescription and has the same meaning as an active component, an effective ingredient, an active substance, or an active ingredient.

In pharmaceutics the term means powder or granule comprised only by a principal agent, or powder or granule mainly including a principal agent when a tablet is produced by compressing a powdered or granular material.

Composition amount of the principal agent is preferably less than or equal to 50 volumes / volume percentage (v/v%) and is more preferably below 20 volumes / volume percentage (v/v%), although it depends on its physical, chemical and pharmacologic property.

When the "principal agent" has peculiar flavor and odor, when it interacts with other component included in a tablet, when a principal agent is preferably transported while being protected to an objective tissue, when it is required to adjust discharge speed, or when it is required to protect a principal agent from environmental factor such as oxygen, water, and light, it is preferable that powder or granule comprised of a principal agent, or powder or granule of which main ingredient is a principal agent is coated with coating agent to achieve these purposes.

A coating method of powder or granule comprised of a principal agent, or powder or granule of which main ingredient is a principal agent isn't specifically limited. For example, several methods such as Pan coating, a fluid-bed coating method or an air-suspension coating may be used.

Powder or granule comprised of a principal agent, or powder or granule of which main ingredient is a principal agent may be powder or granule obtained by grinding a solid dispersing material.

Further when a discharge speed is required to be adjusted, powder or granule comprised of a principal agent, or powder or granule of which main ingredient is a principal agent may be powder or granule which is obtained by grinding a matrix type pharmaceuticals in which a principal agent is dissolved or dispersed homogeneously or non-homogeneously in a high molecular web formation.

When the term only "powder" is used in this specification, it means an aggregation of particle of which diameter (particle size) is greater than or equal to $0.1\mu m$ and less than or equal to $100\mu m$. When the term only "granule" is used, it means an aggregation of particle of which diameter (particle size) is greater than or equal to $100\mu m$. When the term "granulated

material" is used, it means an aggregation in which one particle is comprised of an aggregation of plural particles.

The term "a saccharide with high wettability against water" means a saccharide which is superior in wettablity in water and of which viscosity increase is less when a fixed amount of a saccharide is dissolved in a fixed amount of water.

More specifically, "a saccharide with high wettability against water" means a saccharide which satisfies either kinetic viscosity of a sample solution having density of 1.0g/100ml is less than or equal to 0.92 cm stoke (cSt), or a solubility for water of 25℃ is less than or equal to 18 weight % when measured with the Ubbelohde viscosimeter according to a viscosity measuring method defined by the General Test Procedures of Japanese Pharmacopoeia, 13th edition.

Here it is well known that the wettability of powder layer follows a disintegration model of Washburn and is shown like following experimental formula;

$T = 2\eta L / r \nu \cos\theta$

T : required time for a fixed amount of water to be permeated in powder layer

η: viscosity of permeating water

L: apparent capillary length

r: apparent capillary radius

ν: surface tension of permeating water

θ: angle of contact

When powder layer is a tablet, apparent capillary length L and apparent capillary radius r are decided by density of a tablet. Volume is constant in case of a tablet, so L/r in the above experimental formula can be read as a free volume.

Considering that saccharide has a basically hydrophilic property, the angle of contact θ doesn't become a dominant factor (governing factor) affecting the time T required for permeating a fixed amount of water into a powder layer (tablet), so that the angle of contact θ can be removed from a wettable factor of a powder layer.

Therefore, a viscosity of permeating water η and a surface tension of permeating water ν become a dominant factor (governing factor) affecting the time T required for permeating a fixed amount of water into the powder layer (tablet).

Now considering wettablity of tablet in oral cavity, a solution permeating in tablet is saliva. When saliva is

considered as water, the surface tension of water is 0.85 cm stoke (cSt) (square millimeter/second (mm^2/s)). It can be considered that the surface tension of solution in which a saccharide is dissolved in water doesn't change so much comparing with that of water.

Accordingly it can be said that a dominant factor (governing factor) affecting the time T required for permeating into a powder layer is viscosity of permeating water η.

Therefore, it is preferable that a solution with low viscosity is used in order to shorten the time T required for a fixed amount of water to be permeated in a powder layer (tablet) when a saccharide is dissolved in water.

A saccharide having low solution viscosity was examined by dissolving 0.5g of various kinds of saccharide in 50ml of water.

As the result, powder of trehalose (kinetic viscosity : 0.891cSt), mannitol (kinetic viscosity : 0.896cSt), maltose (kinetic viscosity : 0.896cSt), sorbitol (kinetic viscosity : 0.897cSt), lactose (kinetic viscosity : 0.897cSt), multitol (kinetic viscosity : 0.904cSt), xylitol (kinetic viscosity : 0.904cSt), sucrose (kinetic viscosity : 0.912cSt), erythritol (kinetic viscosity : 0.912cSt), and glucose (kinetic viscosity : 0.895cSt) was granulated while spraying a binder solution by means of spray means according to a fluid-bed granulation method and thus granulated material was compressed and molded as a tablet. It was found by experiments that a tablet using such a saccharide was rapidly disintegrated by saliva in oral cavity.

Further according to experiments, it was found that a tablet produced by compressing the granulated material which used a binder solution in which these saccharide were dissolved or a binder solution in which a surface active agent other than these saccharide was dissolved rapidly disintegrated by saliva in oral cavity comparing with a tablet produced by compressing granulated material using a normal binder solution.

Mannitol is listed up as a saccharide which satisfies the condition that a solubility in water of 25℃ is less than or equals to 18 weight %.

18.19g of mannitol is dissolved in 100ml of water (25℃) and its solubility is about 18 weight/volume% (w/v%) so that mannitol is listed as a group with lowest solubility.

A disintegrant is used for being swollen by the moisture of saliva entered in a tablet so as to help a tablet to be

disintegrated and dispersed into particle level.

Several kinds of disintegrant can be used and it isn't specifically limited.

Crosspovidone, cross sodium carboxymethyl cellulose, low substituted hydroxypropylcellulose, sodium carboxymethylsatarch, sodium alginate, carmellose, sodium carboxymethylcellulose, calsium carboxymethylcellulose, agar powder, gelatin, shellac, crystalline cellulose, calcium carbonate, sodium bicarbonate, starch such as corn starch and potato starch, sodium starch glycolate, tragacanth, methylcellulose (MC), pregelatinized starch (HPS), bentonite, sodium lauryl sulfate, calsium phosphate, povidone are used as disintegrant.

Taking notice of a rapid release of a tablet, crosspovidone, cross sodium carboxymethyl cellulose, low substituted hydroxypropylcellulose, and sodium carboxymethylsatarch are preferable.

Although several kinds of binder can be used, water-soluble polymer is preferably used when considering rapid disintegration of a tablet in oral cavity. For example, there are hydroxypropylcellulose, polyvinylpyrrolidone, hydroxypropylmethylcellulose, partialy saponified polyvinyl alcohol, methylcellulose (HPMC), pullulane, polyvinyl alcohol (PVA), hydroxypropylcellulose (HPC).

Each of particle size of a saccharide with high wettability against water and particle size of a disintegrant is preferably greater than or equal to 10μm to less than or equal to 500 μm, more preferably greater than or equal to 20μm to less than or equal to 300μm, and further preferably greater than or equal to 20μm to less than or equal to 200μm if considering the moldability and disintegration of a tablet in oral cavity.

Granulated material obtained by binding a mixture including at least a principal agent, a saccharide with high wettability against water, and a disintegrant by means of a binder including a saccharide with high wettability against water may be compressed to produce a tablet without adding other components. Or a lubricant, a corrigent, a foaming agent, a diluting agent, a disintegrant auxiliaries, an aromatic, a solubilizing agent, a coloring agent, a fluidizing agent and other adjuvant may be added and thereafter the granulated material may be compressed to produce a tablet.

The amount of adjuvant differs according to expected disintegration time of a tablet and isn't particularly limited. If lubricant is added, the amount of lubricant is preferably greater than or equal to 0.01 weight% and less than or equal to 10 weight%, preferably greater than or equal to 0.1 weight% and less than or equal to 5 weight%, and more preferably 0.5 weight% and less than or equal to 3 weight% for the weight of one produced tablet.

The reason of such limitation is that rapid disintegration which is an original function of the tablet of the present invention is spoiled and the disintegration time becomes slow when the amount of added lubricant exceeds the above range.

On the other hand, when the amount of added lubricant is below the above-mentioned range, a molding material attaches on punches and dies of a tabletting machine so that grinding is caused for the punches and dies and tabletting problems such as sticking, capping, laminating, and binding are easily happened, thereby deteriorating productivity.

Lubricant isn't limited and several kinds of lubricant may be used, for example, stearic acid, salt stearate (Al, K, Na, Ca, Mg), stearyl alcohl, sucrose esters of fatty acid, talc, carnauba wax, light anhydrous silicic acid, magnesium silicate, synthetic aluminum silicate, hardened oil, white beeswax, titanium oxide, talc, corn starch, microcrystalline cellulose, macrogol 4000, macrogol 6000, isopropyl myristate, magnesium lauryl sulfate, dibasic calsium phosphate, and wax.

An adjuvant among the above-mentioned other than a lubricant varies according to the physical and chemical property of principal agent, the object of a tablet, and the size of a tablet so that it is difficult to define generally. However, the amount of such adjuvant is preferably minimum. It is because that the function of granulated material is spoiled and the function of other component is dominant when a large amount of such adjuvant is added for a granulated material.

Further, a corrigent isn't limited and several kinds of sweetening agent and several kinds of flavoring agent are used. Sweetening agent is, for example, aspartame, saccharin, saccharin sodium, glycyrrhizin (glycyrrhizic acid), trisodium glycyrrhizinate, disodium glycyrrhizinate, powdered sweet hydrangea leaf, glycyrrhiza (powder, extract), syrup, sucrose, honey, and D-mannitol. A flavoring agent is, for example, cacao

butter, citric acid, monosodium glutaminate, tartaric acid, and ginger other than several kinds of aromatic agent and several kinds of sweetening agent.

A forming agent isn't limited and several kinds can be used, for example, sodium bicarbonate, sodium carbonate, and calcium carbonate.

A diluting agent isn't limited and several kinds can be used, for example, lactose, corn starch, and crystalline cellulose.

A disintegrant isn't limited and several kinds can be used, for example, solubilizing agent, emulsifier, suspension and dispersant.

A solubilizing agent isn't limited and several kinds can be used, for example, sodium oleate, polyoxil stearate, propylene carbonate, polyoxyethylene lauryl ether, polysorbate 80, isopropyl myristate, and lauromacrogol.

An emulsifier isn't limited and several kinds can be used, for example, acacia gum, cholesterol, sodium carboxymethylcellulose, polyoxil stearate 40, sorbitan sesquioleate, methylcellulose (HPMC), BEGUM (aluminum magnesium silicate, "BEGUM" is a registered trademark of Sansho Co., Ltd.), bentonite, polysorbate 80, aluminum monostearate, medicinal soap, sodium lauryl sulfate, lauromacrogol, and lecithin.

A suspension isn't limited and several kinds can be used, for example, acacia gum, sodium alginate, methylcellulose (MC), sodium carboxymethylcellulose, tragacanth, bentonite, polysorbate 80, polyvinylpyrrolidone, and aluminum monostearate.

A dispersant isn't limited and several kinds can be used, for example, glycerin, sodium carboxymethylcellulose, sucrose solution, polysorbate 80, D-mannitol, and aluminum monostearate.

An aromatic isn't limited and several kinds can be used, for example, lemon oil, orange oil, fruit juice extract such as lemon, orange, and pine, menthol, fennel oil, cinnamon oil, saffron, spearmint, mentha water, vanilla, peppermint oil, bergamot oil, rose oil, eucalyptus oil, and aromatic water.

A solubilizing agent is, for example, ethylenediamine, sodium benzoate, meglumine, and glycerin.

A coloring agent isn't limited and several kinds can be used, for example, erythrosine (red No.3), rose bengale (red No.105),

tartrazine (yellow No.4), fast green FCF (green No.3), indigocarmine (blue No.2), all of which are tar color defined by the Health and Welfare Ministry, iron dioxide (yellow coloring agent), iron oxide (red coloring agent), caramel, β -carotene, bengala ($Fe2O3$), riboflavin, and medicinal carbon.

In order to bring out the function of rapid disintegration of tablet to the fullest according to the present invention, it is desirable not to add a lubricant in a granulated material at all before compressing a granulated material obtained by mixing mixture of a principal agent, a saccharide with high wettability against water, and a disintegrant with a binder including a saccharide with high wettability against water.

It is preferable to use an external lubricant spraying method in order to produce a tablet without adding a lubricant in a granulated material, without adhering a molding material on the punches and dies of a tabletting machine, and without causing tabletting problems such as sticking (refer to JP-A-56-14098, JP-A-59-205970, JP-A-3-9757, JP-A-4-295366, JP-A-5-318198, JP-A-8-281492, JP-A-8-19589, JP-A-7-124231).

Such a tablet is characterized in that the particle of mixture is bound with a binder including a saccharide with high wettability against water without by a normal binder when a mixture powder including a saccharide with high wettability against water and a disintegrant is granulated.

The tablet uses a saccharide with high wettability against water so that it can be rapidly disintegrated by saliva in oral cavity.

Further, the particle of a granulated material is bound by a binder including a saccharide with high wettability against water. Accordingly, when the tablet is given in oral cavity, a saccharide with high wettability against water in a binder gets wet by saliva in oral cavity and is dissolved or dispersed in saliva. As a result, the binding force of binder particle becomes weak and the granulated material is decayed so that the tablet is rapidly disintegrated.

On the other hand, as the particle comprising a tablet is bound by a binder and the binding force is strong, the tablet doesn't get chipped while storage and transportation.

Further according to such a tablet, functional coating (for example enteric coating) may be executed for granule including a principal agent in such a manner that a principal agent is

dissolved at an objected part, sustained release coating is executed so that the tablet is dissolved gradually, solid dispersing granule may be prepared so as not to crystallize a principal agent, or a principal agent may be granule dispersed in a wax matrix construction so that rapidly disintegrable medicine in oral cavity can be achieved.

(2) The present invention relates to a tablet obtainable by binding a mixture powder including at least a principal agent, a saccharide with high wettability against water, a saccharide with high moldability, and a disintegrant by means of a binder including a saccharide with high wettability against water.

According such a tablet, the saccharide with high moldability is further added in a molding material as set forth in claim 1 considering the moldability of a tablet.

At least one of saccharide with high moldability selected from the group comprising lactose, maltitol, sorbitol, and oligosaccharide can be used.

Considering the moldability and disintegration of a tablet in oral cavity, the particle size of the saccharide with high moldability is preferably greater than or equal to 10μm and less than or equal to 500μm, more preferably greater than or equal to 20μm and less than or equal to 300μm, still more preferably greater than or equal to 20μm and less than or equal to 200μm.

Such a tablet uses a saccharide with high wettability against water so that it can be rapidly disintegrated in oral cavity.

Further, the particle of granulated material is bound by a binder including a saccharide with high wettability against water. Accordingly, when the tablet is given in oral cavity, the saccharide with high wettability against water in the binder gets wet by saliva in oral cavity and is dissolved or dispersed in saliva. As a result, the binding force of the binder particle becomes weak and the granulated material is decayed so that the tablet is rapidly disintegrated.

Still further, such a tablet includes the particle of saccharide with high moldablity so that the moldability in case of compressing is excellent. Therefore, the tablet doesn't get chipped when it is compressed and while storage and transportation, achieving superior characteristic.

Further according to such a tablet, functional coating (for

example enteric coating) may be executed for the granule including a principal agent in such a manner that the principal agent is dissolved at an objected part, sustained release coating is executed so that the tablet is dissolved gradually, a solid dispersing granule may be prepared so as not to crystallize principal agent, or a principal agent may be a granule dispersed in a wax matrix construction so that the tablet doesn't get chipped when it is compressed and while storage and transportation, thereby achieving rapid disintegrable medicine in oral cavity.

(3) The present invention relates to a tablet characterized in that the ratio of the saccharide with high wettability against water and the saccharide with high moldability included in the granulated material of the tablet of claim 2 is such that the saccharide with high wettability against water is greater than or equal to 60 volume percentage and less than or equal to 90 volume percentage and the rest is saccharide with high moldability.

Namely, the volume ratio of the blended saccharide with high wettability against water and the saccharide with high moldability is within the range of 6:4 to 9:1.

More detailed, when the saccharide with high wettability against water and the saccharide with high moldability are extracted from several kinds of component included in the tablet and sum volume of them is set as 100 volume%, the saccharide with high wettability against water is greater than or equal to 60 volume% and less than or equal to 90 volume% and the rest volume% is a saccharide with high moldability.

More preferably, the particle of saccharide with high wettability against water is greater than or equal to 60 volume% and less than or equal to 80 volume%, more preferably greater than or equal to 60 volume% and less than or equal to 70 volume%.

According to such a tablet, the blend ratio of the particle of the wettable sacharide and the particle of the saccharide with high moldability is set in such a manner that the tablet which is excellent in the moldability of compression and is rapidly disintegrated in oral cavity can be produced. Therefore, the tablet rapidly disintegrable in oral cavity can be produced at high productivity.

(4) The present invention relates to a tablet wherein the saccharide with high moldability used in the tablet of claim

2 or 3 is at least one member selected from the group comprising lactose, maltitol, sorbitol, and oligosaccharide.

According to such a tablet, the saccharide which is excellent in safety and moldability and is available is selected as a saccharide with high moldability so that a tablet excellent in safety, moldability and rapidly disintegrable in oral cavity can be easily produced

(5) The present invention relates to a tablet wherein the saccharide with high wettability against water used in the tablet of claims 1 - 4 is one member selected from the group comprising trehalose, mannitol, maltose, sorbitol, lactose, multitol, xylitol, sucrose, erythritol, and glucose.

According to such a tablet, the saccharide which is excellent in safety and wettability and is easily available is selected as a saccharide with high wettability against water, so that a tablet which has excellent safety and is rapidly disintegrated in oral cavity can be easily produced.

Further, because the viscosity of the solution of saccharide with high wettability against water isn't increased when being dissolved in water, water in saliva is easily permeated in a tablet. The tablet is rapidly dissolved by saliva in oral cavity because of such function.

(6) The present invention relates to a tablet wherein a surface active agent is included in a binder used in the tablet of claims 1 - 5.

Anionic surface-active agents, cationic surfactant, nonionic surfactant, amphoteric surfactant may be used as surface active agent, or high molecular surface active agent such as Pluron or Poloxamer may be used.

More concretely, preferable example of anionic surface-active agents is sulfates ($R \cdot O \cdot SO_3^- \cdot M^+$) such as sodium lauryl sulfate.

Preferable example of nonionic surfactant is sorbitan esters and polysorbates, of which preferable example is polysorbate 80.

A surface active agent of which HLB (hydrophile-lipophile balance) is greater than or equal to 10 and less than or equal to 40 is preferable.

According to such a tablet, the particles are bound by a binder including a surface active agent other than a saccharide with high wettability against water.

Therefore, the binder is easily wettable because the boundary tension of water in saliva is lowered by a surface active agent in binder when the tablet is in oral cavity. Then a saccharide with high wettability against water gets quickly wet and dissolved or dispersed in saliva from a binder. Accordingly the binding force of a binder is lost and a granulated material is dissolved rapidly.

(7) The present invention relates to a tablet wherein a binder used for the tablet in claim 1 - 6 is a water-soluble polymer.

A water-soluble polymer isn't limited if it is soluble in water and is harmless for human body. Several kinds can be used, for example polyvinyl alcohol, polyethylene oxide, and polyvinylpyrrolidone.

According to such a tablet, the particle of granule is bound by a water-soluble polymer including a saccharide with high wettability against water. Therefore, a binder is permeated in water in saliva when it contacts saliva in oral cavity. As a result, because a granulated material is quickly disintegrated and dispersed into particle level, the tablet can be rapidly disintegrated in oral cavity.

Further according to the tablet, the particle of saccharide with high wettability against water is dispersed in a water-soluble polymer binding the particle comprising the granulated material. According to such a tablet, the particle of saccharide with high wettability against water dispersed in a water-soluble polymer is dissolved into saliva when it contacts saliva in oral cavity. According to such construction, when the tablet is in oral cavity, a saccharide with high wettability against water in a binder quickly gets wet by saliva therein and dissolved or dispersed in saliva. As a result, the particle binding force of binder becomes weak so that such tablet is rapidly disintegrated comparing with the tablet in which the particle comprising granule is bound by a water-soluble polymer.

(8) The present invention relates a method of producing a tablet comprising the steps of making a fluidized bed prepared by mixing a powdered mixture prepared by mixing at least a principal agent, a saccharide with high wettability against water, and a disintegrant homogenously with air; producing a granulated material including a principal agent by spraying aqueous solution, in which a binder and a saccharide with high wettability against water are dissolved, into the fluidized

powdered mixture and drying the granulated material; and compressing the granulated material including the principal agent to be tabletted.

According to such a production method, an intrabuccally rapidly disintegrable tablet can be produced by means of a fluid bed granulation method and a compression mold method which are generally used for producing a normal tablet so that a new and particular apparatus isn't required for producing an intrabuccally rapidly disintegrable tablet.

According to the tablet produced by such a production method, a granulated material included therein is bound by a binder including a saccharide with high wettability against water. Therefore, it is superior in disintegrability in oral cavity comparing with the tablet in which a granulated material using only a binder is compressed.

(9) The present invention relates to a method of producing a tablet comprising the steps of; making a fluidized bed by mixing a powdered mixture prepared by mixing at least a principal agent, a saccharide with high wettability against water, a saccharide with high moldability, and a disintegrant homogenously with air; producing a granulated material including a principal agent by spraying an aqueous solution in which a binder and a saccharide with high wettability against water are dissolved into the fluidized powdered mixture and drying the granulated material; and compressing the granulated material including the principal agent to be tabletted.

Also according to this production method, an intrabuccally rapidly disintegrable tablet can be produced by means of a fluid bed granulation method and a compression molding method which are generally used for producing a normal tablet so that a new and particular apparatus isn't required for producing an intrabuccally rapidly disintegrable tablet.

In the tablet produced by such a production method, the particle comprising a granulated material included therein is bound by a binder including a saccharide with high wettability against water. Therefore, it is superior in disintegrability in oral cavity comparing with the tablet in which a granulated material using a binder including only water-soluble polymer is compressed.

Further according to this production method, the particle of saccharide with high moldability is included in a granulated

material. Thereby, tabletting problems such as sticking aren't caused for the produced tablet.

(10) The present invention relates to a method for producing a tablet, wherein a surface active agent is further added in the aqueous solution including a binder and a saccharide with high wettability against water as set forth in claim 8 or 9.

According to this production method, a surface active agent is added in a binder. Therefore, in the tablet produced by this method, the particle comprising a granulated material included in a tablet is bound by a binder including a surface active agent other than a saccharide with high wettability against water so that such a tablet is more rapidly disintegrated in oral cavity.

(11) The present invention relates to a method for producing a tablet wherein the binder used in any one of claims 8 - 10 is water-soluble polymer.

According to this production method, a water-soluble polymer is used as a binder and the binder is dissolved in water in saliva when the tablet produced by this production method touches saliva in oral cavity. Therefore, a granulated material is quickly dissolved and dispersed into particle level and rapidly disintegrated in oral cavity.

Further according to such a tablet, the particle of saccharide with high wettability against water is dispersed in water-soluble polymer binding the particle comprising a granulated material. Therefore, when such a tablet produced by this production method touches saliva in oral cavity, the particle of saccharide with high wettability against water dispersed in a water-soluble polymer is dissolved in saliva. According to such construction, when the tablet is given in oral cavity, a saccharide with high wettability against water in a binder quickly gets wet and dissolved or dispersed in saliva. Therefore, the binding force of particle in the binder becomes weak and a granulated material is disintegrated so that the table is rapidly disintegrated.

(12) The present invention relates to a method for producing a tablet wherein the aqueous solution including a binder and a saccharide with high wettability against water in claim 11 is adjusted in such a manner that a binder is greater than or equal to 1 volume and less than or equal to 3 volumes for water of 100 volumes and the volume of the saccharide with high wettability against water is greater than or equal to 5 volumes

and less than or equal to 6 volumes for water of 100 volumes.

According to this production method, the ratio of the binder and the saccharide with high wettability against water included in the aqueous solution used for granulation is adjusted in such a manner that the compressed tablet has practical hardness and the tablet is rapidly dissolved in oral cavity. Therefore, an intrabuccally rapidly disintegrable tablet which is hardly chipped during storage and transportation and is rapidly dissolved in oral cavity can be produced.

Brief Description of Drawings

Fig.1 is an explanatory view diagrammatically showing one preferable embodiment of a granulated material used in the tablet (an intrabuccally rapidly disintegrable tablet) of the present invention.

Fig.2 is a process drawing schematically showing one embodiment of a production procedure of the tablet (an intrabuccally rapidly disintegrable tablet) of the present invention.

Fig.3 is a process drawing schematically showing one embodiment of a production procedure of the tablet (an intrabuccally rapidly disintegrable tablet) of the present invention.

Fig.4 is an explanatory view diagrammatically showing how the tablet (an intrabuccally rapidly disintegrable tablet) Ta of the present invention is disintegrated in oral cavity. Fig.4(a) is a perspective view of the tablet (an intrabuccally rapidly disintegrable tablet), Fig.4(b) is a diagrammatic view in which the area R1 in Fig.4(a) is enlarged, Fig.4(c) is a diagrammatic view in which the area R2 in Fig.4(b) is enlarged, and Fig.4(d) is a diagrammatic view showing how the tablet (intrabuccally rapidly disintegrable tablet) is disintegrated in saliva.

Fig.5 is an explanatory view diagrammatically showing another preferable embodiment of a granulated material used in the tablet (intrabuccally rapidly disintegrable tablet) of the present invention.

Fig.6 is a process drawing schematically showing one embodiment of a production procedure of the tablet (an intrabuccally rapidly disintegrable tablet) of the present invention.

Fig.7 is a process drawing schematically showing one embodiment of a production procedure of the tablet (an intrabuccally rapidly disintegrable tablet) of the present invention.

Fig.8 diagrammatically shows a disintegration procedure of the tablet (an intrabuccally rapidly disintegrable tablet) in oral cavity. Fig.8(a) is a perspective view of the tablet (an intrabuccally rapidly disintegrable tablet), Fig.8(b) is a diagrammatic view in which the area R3 in Fig.8(a) is enlarged, Fig.8(c) is a diagrammatic view in which the area R4 in Fig.8(b) is enlarged, and Fig.8(d) is a diagrammatic view showing how the tablet (intrabuccally rapidly disintegrable tablet) is disintegrated in saliva.

Fig.9 is an explanatory view diagrammatically showing still another preferable embodiment of a granulated material used in the intrabuccally rapidly disintegrable tablet of the present invention.

Fig.10 is a process drawing schematically showing another embodiment of a production procedure of the tablet (intrabuccally rapidly disintegrable tablet) of the present invention.

Fig.11 is a process drawing schematically showing another embodiment of a production procedure of the tablet (intrabuccally rapidly disintegrable tablet) of the present invention.

Fig.12 diagrammatically shows a disintegration procedure of the tablet (intrabuccally rapidly disintegrable tablet) in oral cavity. Fig.12(a) is a perspective view of the tablet (an intrabuccally rapidly disintegrable tablet), Fig.12(b) is a diagrammatic view in which the area R5 in Fig.12(a) is enlarged, Fig.12(c) is a diagrammatic view in which the area R6 in Fig.12(b) is enlarged, and Fig.12(d) is a diagrammatic view showing how the tablet (an intrabuccally rapidly disintegrable tablet) is disintegrated in saliva.

Fig.13 shows a diagrammatic entire construction of an external lubricant spraying type tabletting machine used for producing the tablet of the present invention.

Fig.14 is a plane view of a rotary-type tabletting machine of the external lubricant spraying type tabletting machine in Fig.13.

Fig.15 is an explanatory view of a pulsating vibration air

generation means comprising the external lubricant spraying type tabletting machine in Fig.13.

Fig.16 is a diagrammatic sectional view of discharge means (quantitative feeder) comprising the external lubricant spraying type tabletting machine in Fig.13.

Fig.17 is a plane view diagrammatically showing an elastic membrane used for the discharge means (quantitative feeder) in Fig.16.

Fig.18 is a view explaining operations of the elastic membrane in Fig.17.

Fig.19 is a plane view diagrammatically showing the construction of a lubricant spraying means comprising the external lubricant spraying type tabletting machine in Fig.13.

Fig.20 is an outer perspective view diagrammatically showing an upper punch lubrication means of the lubricant spraying means in Fig.19 when seen from the periphery of the rotary table into the center thereof.

Fig.21 shows a diagrammatic section along the line I-I in Fig.19.

Fig.22 shows a diagrammatic section along the line II-II in Fig.19.

Best Mode for Carrying Out the Invention

(Embodiment of the Invention 1)

Fig.1 is an explanatory view diagrammatically showing one preferable embodiment of a granulated material used in the tablet (intrabuccally rapidly disintegrable tablet) of the present invention.

A granulated material 1a is comprised such that a mixed powder (particle) 5a including a principal agent (particle) 2 ···, particle 3 ··· of a saccharide with high wettability against water, and a disintegrant particle 4 ··· are bound by a binder 6 ···including a water-soluble molecular 7 and the particle (precipitation of fine particle) 8 ··· of a saccharide with high wettability against water.

More detailed, the binder 6 is constructed such that the particle (precipitation of fine particle) 8 ··· of a saccharide with high wettability against water is dispersed in a water soluble polymer 7.

When a binder solution added with the particle (precipitation of fine particle) 8 ··· of a saccharide with high

wettability against water is dried, the saccharide with high wettability against water included in the solution is separated out to be the particle (precipitation of fine particle) 8 ··· of a saccharide with high wettability against water.

Particle or granule including an active agent or granule including medicinal properties coated with functional coating, granule in which an active agent is dispersed in a wax matrix construction, or solid dispersing granule may be used as an principal agent (particle) 2.

The particle diameter of the principal agent (particle) 2 is greater than or equal to 10μm and less than or equal to 500 μm, more preferably greater than or equal to 20μm and less than or equal to 300μm, still more preferably greater than or equal to 20μm and less than or equal to 200μm.

The granulated material 1a using principal agent (particle) 2 within the above-mentioned range is easily tabletted and the tablet (Ta shown in Fig.3) produced by compressing the granulated material 1a is excellent at disintegration in oral cavity.

At least one member selected from the group comprising trehalose, mannitol, maltose, sorbitol, lactose, multitol, xylitol, sucrose, erythritol, and glucose may be used as the particle 3 of a saccharide with high wettability against water.

The particle diameter of the particle 3 of a saccharide with high wettability against water is also greater than or equal to 10μm and less than or equal to 500μm, more preferably greater than or equal to 20μm and less than or equal to 300μm, still more preferably greater than or equal to 20μm and less than or equal to 200μm.

The granulated material 1a using the particle 3 of a saccharide with high wettability against water within the above-mentioned range is easily tabletted and the tablet Ta produced by compressing the granulated material 1a is excellent at disintegration in oral cavity.

Sodium alginate, carmellose, sodium carboxymethyl-cellulose, calsium carboxymethyl-cellulose, agar powder, gelatin, shellac, crystalline cellulose, calcium carbonate, sodium bicarbonate, starch such as corn starch and potato starch, sodium starch glycolate, tragacanth, methylcellulose (MC), pregelatinized starch (HPS), bentonite, sodium lauryl sulfate, calsium phosphate, povidone may be used as a disintegrant

(particle) 4.

The particle diameter of the disintegrant (particle) 4 is also greater than or equal to 10μm and less than or equal to 500μm, more preferably greater than or equal to 20μm and less than or equal to 300μm, still more preferably greater than or equal to 20μm and less than or equal to 200μm.

The granulated material 1a using the disintegrant (particle) 4 within the above-mentioned range is easily tabletted and the tablet Ta produced by compressing the granulated material 1a is excellent at disintegration in oral cavity.

The granulated material 1a is characterized in that the mixed powder (particle) 5a including a principal agent 2, the particle 3 of a saccharide with high wettability against water, and a disintegrant particle 4 is bound by a binder 6 including the particle (precipitation of fine particle) 8 ··· of a saccharide with high wettability against water.

A water-soluble polymer 7 used for the binder 6 isn't limited if it is a normal water-soluble polymer as binder, for example, polyvinyl alcohol (PVA), hydroxypropylcellulose (HPC), and hydroxypropyl-methylcellulose (HPMC). One of them is used or more than two of them may combined and used.

At least one member selected from the group comprising trehalose, mannitol, maltose, sorbitol, lactose, multitol, xylitol, sucrose, erythritol, and glucose may be used as the particle (precipitation of fine particle) 8 ··· of a saccharide with high wettability against water to be included in the binder 6.

Fig.2 and Fig.3 are process drawings schematically showing one embodiment of a production procedure of the intrabuccally rapidly disintegrable tablet of the present invention.

In the procedure in Fig.2(a), a mixed powder (particle) 5a is prepared by homogeneously mixing a principal agent 2, the particle 3 of saccharide with high wettability against water and a disintegrant particle 4 by a mixer.

Then, a binder solution for granulating the mixed powder (particle) 5a is adjusted as shown in Fig.2(b).

The binder solution for granulating the mixed powder (particle) 5a is adjusted in such a manner that the water-soluble polymer and the saccharide with high wettability against water are dissolved in water.

More detailed, the binder solution used for granulating the mixed powder (particle) 5a is adjusted in such a manner that the water-soluble polymer is greater than or less than 1 volume% and les than 3 volume% for 100 volume% of water and the saccharide with high wettability against water is greater than or equal to 5 volume% and less than or equal to 6 volume% for 100 volume% of water.

In case of an aqueous solution including greater than or equal to 3 volume% of water-soluble polymer, the density of binder solution used for a normal tablet becomes such that the water-soluble polymer is greater than or equal to 3 volume% and less than or equal to 5 volume%. The binding force of the principal agent (particle) 2 ···, the particle 3 ··· of saccharide with high wettability against water and the disintegrant (particle) 4 ···, all comprising the granulated material 1a, becomes similar to the binding force of a normal tablet and the disintegration time in oral cavity becomes slower comparing with the case that the water-soluble polymer is adjusted to be less than 3 volume%.

If the water-soluble polymer 1 in the binder solution used for granulating the mixed powder 5a is less than 1 volume%, the binding force of the principal agent (particle) 2 ···, the particle 3 ··· of saccharide with high wettability against water and the disintegrant (particle) 4 ···, all comprising the mixed powder 5a, becomes weak like the case when a water-soluble polymer isn't used at all for an aqueous solution for granulating the mixed powder 5a (for example only water or ethanol is used as a binder). Therefore, the moldability of compression becomes worse and the hardness of the compressed tablet becomes lower than the practical hardness so that the tablet may be easily chipped while storage and transportation.

As shown in Fig.2(c), the mixed powder (particle) 5a obtained in the procedure in Fig.2(a) is stored in a granulation tank 11 of a fluid layer granulation means and is fluidized by being mixed with a heated air according to a general method. Then the aqueous solution in which a water-soluble polymer and a saccharide with high wettability against water are adjusted in the procedure Fig.2(b) and dissolved is sprayed from a spraying means 12 to the fluidized mixed powder (particle) 5a, they are dried and produced to be a granulated material having an intended particle size and particle distribution

(aggregation of granulated material 1a shown in Fig.1).

In Fig.2(c), the numeral 11a shows a heated air supply port, and 11b is a discharge port for discharging a heated air supplied in the granulation tank 11 to outside.

Further, the numeral 13 shows a porous screen, 14 is a binder solution tank, 15 is a binder solution supply means for supplying a binder solution stored in the binder solution tank 14 to the spraying means 12, 16 is a dust collection filter, 17 is a dust collection filter vibration means for vibrating the dust collection filter 16 for dropping the powder, the granulated material, or the material under granulation attached on the dust collection filter 16, 18 is an air source such as a blower for supplying compressed air for spraying a binder solution from the spray means 12 and supplying a compressed air for driving the dust collection filter vibration means.

Then, in the procedure shown in Fig.3(a), thus a produced granulated material 1a is compressed and molded by means of an upper punch 21, a die 22, and a lower punch 23 of the rotary tabletting machine and an intrabuccally rapidly disintegrable tablet Ta is produced (See Fig.3(b)).

Lubricant may be added in the granulated material 1a ··· and the tablet Ta (intrabuccally rapidly disintegrable tablet) may be produced in order to smoothly execute continuous tabletting as a pre-procedure before the procedure shown in Fig.3(a).

Or lubricant may be coated on each surface of the upper punch 21, the die 22, and the lower punch 23 of the tabletting machine and granulated material 1a ··· may be compressed by means of thus lubricated upper punch21, die 22, and lower punch 23 without adding a lubricant in the granulated material 1a ···, thereby tablet Ta (intrabuccally rapidly disintegrable tablet) may be produced.

Further, one or more than two of an acidifier such as citric acid, tartaric acid, and malic acid, a foaming agent such as baking soda, an artificial sweetener such as dipotassium glycyrrhizinate, aspartame, stevia, and thaumatin, a perfume such as lemon, lemon lime, orange, and menthol, a coloring agent such as food yellow No.5, food red No.2, food blue No.2 may be added if required in the procedure of producing a mixed powder (particle) 5a.

The member shown as 24 in Fig.3(a) is a part of a rotary table of the rotary type tabletting machine.

Fig.4 is an explanatory view diagrammatically showing how the tablet Ta (intrabuccally rapidly disintegrable tablet) is disintegrated in oral cavity. Fig.4(a) is a perspective view of the tablet Ta (intrabuccally rapidly disintegrable tablet), Fig.4(b) is a diagrammatic view in which the area R1 in Fig.4(a) is enlarged, Fig.4(c) is a diagrammatic view in which the area R2 in Fig.4(b) is enlarged, and Fig.4(d) is a diagrammatic view showing how the tablet Ta (intrabuccally rapidly disintegrable tablet) is disintegrated in saliva.

According to this tablet Ta (intrabuccally rapidly disintegrable tablet), the binding between the particles 2 ···, 3 ···, 4 ··· of the granulated material 1a ··· included in the tablet Ta is achieved by a binder 6 including a water-soluble polymer 7 and the particle (precipitation of fine particle) 8 ··· of saccharide with high wettability against water.

Therefore, when the tablet Ta doesn't touch water, the particles 2 ···, 3 ···, 4 ··· are bound by a water soluble polymer 7 so that each granulated material 1a is hardly broken like a normal tablet. Thereby, the tablet Ta is hardly chipped while storage and transportation.

On the other hand as shown in Fig.4(d), when the tablet Ta is given in oral cavity, a disintegrant 4 is swollen by water in saliva and the granulated material 1a is disintegrated into particle level comprising the granulated material 1a.

The fact that the tablet is disintegrated into a particle level comprising the granulated material 1a by a disintegrant 4 is the same as the prior intrabuccally rapidly disintegrable tablet. However according to the tablet Ta, the particle (precipitation of fine particle) 8 ··· of saccharide with high wettability against water is dispersed therein. Accordingly, the tablet Ta easily get wet in water in saliva in oral cavity comparing with the tablet wherein a binder 6 is comprised of only a water-soluble polymer 7 (namely, the particle (precipitation of fine particle) 8 ··· of saccharide with high wettability against water isn't included in the binder 6). Thereby, the particle (precipitation of fine particle) 8 ··· of saccharide with high wettability against water gets wet in water in saliva in oral cavity, dispersed or dissolved therein, then the physical strength of the water-soluble polymer 7 becomes weak and the surface area of water-soluble polymer 7 is enlarged. As a result, the water-soluble polymer 7 rapidly gets wet in

water in saliva in oral cavity and is dispersed and dissolved therein.

Further according to the tablet Ta, the particle 3 ··· of saccharide with high wettability against water is used as particle comprising a granulated material 1a and the particle (precipitation of fine particle) 8 ··· of saccharide with high wettability against water is dispersed in a binder 6.

Herewith, the particle of saccharide with high wettability against water included in each granulated material 1a ··· is also dissolved or dispersed in saliva so that the tablet Ta (intrabuccally rapidly disintegrable tablet) is quickly disintegrated in oral cavity.

Further, when the particle 3 of saccharide with high wettability against water and the particle (precipitation of fine particle) 8 ··· of saccharide with high wettability against water are dissolved in saliva, they don't make the viscosity of saliva η in which they are dissolved high comparing with the viscosity of water η w. Thereby, when the particle 3 of saccharide with high wettability against water and the particle (precipitation of fine particle) 8 ··· of saccharide with high wettability against water are dissolved in saliva, the viscosity of saliva doesn't become high so that saliva is quickly permeated in the tablet Ta. The tablet Ta is rapidly disintegrated in oral cavity also because of such function.

(Embodiment of the Invention 2)

Fig.5 is an explanatory view diagrammatically showing another preferable embodiment of a granulated material used in the tablet (intrabuccally rapidly disintegrable tablet) of the present invention.

A granulated material 1b is constructed the same as the granulated material 1a explained in the embodiment of the invention 1 excluding that a saccharide particle with high moldability 9 ··· is included so that the corresponding particle is allotted with the corresponding reference numeral and their explanations are omitted.

The granulated material 1b is comprised such that a mixed particle 5b including a principal agent (particle) 2 ···, a particle 3 of saccharide with high wettability against water, a disintegrant particle 4 ···, and a saccharide particle with high moldability 9 ··· are bound by a binder 6 ··· including a

water-soluble molecular 7 and the particle (precipitation of fine particle) 8 ··· of saccharide with high wettability against water.

The binder 6 is constructed such that the particle (precipitation of fine particle) 8 ··· of saccharide with high wettability against water is dispersed in the water soluble polymer 7.

The granule including an active agent or the granule including medicinal properties coated with functional coating, the granule in which an active agent is dispersed in a wax matrix construction, or solid dispersing granule may be used as a principal agent (particle) 2.

One member selected from the group comprising lactose, maltitol, sorbitol, and oligosaccharide may be used as a saccharide particle 9 with high moldability.

The particle diameter of the saccharide with high moldability 9 (particle) is greater than or equal to 10μm and less than or equal to 500μm, more preferably greater than or equal to 20μm and less than or equal to 300μm, still more preferably greater than or equal to 20μm and less than or equal to 200μm.

The granulated material 1b using the saccharide with high moldability 9 (particle) within the above-mentioned range is easily tabletted and the tablet (Tb shown in Fig.7) produced by compressing the granulated material 1b is excellent at disintegration in oral cavity.

The material of saccharide 3 is the same as the saccharide with high wettability against water 3 used for the granulated material 1a, so its explanation is omitted here.

The ratio of the particle 3 of saccharide with high wettability against water and the saccharide particle with high moldability 9 is such that the particle 3 of saccharide with high wettability against water is preferably greater than or equal to 60 volume percentage and less than or equal to 90 volume percentage, more preferably greater than or equal to 60 volume percentage and less than or equal to 80 volume percentage, still more preferably greater than or equal to 60 volume percentage and less than or equal to 70 volume percentage when the sum of the particle 3 of saccharide with high wettability against water and the saccharide particle with high moldability 9 is set at 100 volume%.

If a saccharide particle with high moldability 9 exceeds 40 volume%, tabletting problems in case of compression (for example sticking, laminating or capping) are reduced, however, disintegration in oral cavity becomes a little slower comparing with the case when it is less than or equal to 40 volume%.

If a saccharide particle with high moldability 9 is less than 10 volume%, disintegration in oral cavity is the same as the case when it is greater than or equal to 10 volume%, however, the moldability in case of compression becomes a little worse comparing with the case when it is greater than or equal to 10 volume%.

The material of disintegrant 4 is the same as the disintegrant 4 used for the granulated material 1a, so its explanation is omitted here.

The granulated material 1b is characterized in that the mixed powder (particle) 5b including a principal agent 2, the particle 3 of saccharide with high wettability against water, the saccharide particle with high moldability 9 and a disintegrant (particle) 4 is bound by a binder 6 including a water-soluble polymer 7 and the particle (precipitation of fine particle) 8 ··· of saccharide with high wettability against water.

The material of water-soluble polymer 7 used for a binder 6 is also the same as the water-soluble polymer 7 used for the granulated material 1a so that its explanation is omitted here.

The material of the particle (precipitation of fine particle) 8 ··· of saccharide with high wettability against water used for a binder 6 is the same as the particle (precipitation of fine particle) 8 ··· of saccharide with high wettability against water used for the granulated material 1a so that its explanation is omitted here.

Fig.6 and Fig.7 are process drawings schematically showing one embodiment of a production procedure of the intrabuccally rapidly disintegrable tablet of the present invention.

In the procedure in Fig.6(a), a mixed powder (particle) 5b is prepared by homogeneously mixing a principal agent (particle) 2, the particle 3 of saccharide with high wettability against water, a disintegrant particle 4, and the saccharide particle with high moldability 9 by a mixer.

Here the ratio of the particle 3 of saccharide with high wettability against water and the saccharide particle with high

moldability 9 is adjusted in such a manner that the particle 3 of saccharide with high wettability against water is greater than or equal to 60 volume% and less than or equal to 90 volume%.

Then, a binder solution for granulating the mixed powder (particle) 5b is adjusted as shown in Fig.6(b).

The binder solution for granulating the mixed powder (particle) 5b is the same as the binder solution used for the embodiment of the invention 1, so its explanation is omitted here.

As shown in Fig.6(c), mixed powder (particle) 5b obtained in the procedure in Fig.6(a) is stored in a granulation tank 11 of a fluid layer granulation means and is fluidized by being mixed with heated air according to a general method. Then aqueous solution in which a water-soluble polymer and a saccharide with high wettability against water are adjusted in the procedure Fig.6(b) and dissolved is sprayed from a spraying means 12 to the fluidized mixed powder (particle) 5b, they are dried and produced to be granulated material having an intended particle size and particle distribution (aggregation of granulated material 1b shown in Fig.5).

Then, in the procedure shown in Fig.7(a), thus produced granulated material 1b is compressed and molded and the tablet Tb (intrabuccally rapidly disintegrable tablet) is produced (See Fig.7(b)).

A lubricant may be added in the granulated material 1b ··· and the intrabuccally rapidly disintegrable tablet Tb may be produced in order to smoothly execute continuous tabletting as a pre-procedure before the procedure shown in Fig.7(a).

Or a lubricant may be coated on each surface of the upper punch 21, the die 22, and the lower punch 23 of the tabletting machine and the granulated material 1b ··· may be compressed by means of thus lubricated upper punch 21, die 22, and lower punch 23 without adding a lubricant in the granulated material 1b ···, thereby the tablet Tb (intrabuccally rapidly disintegrable tablet) may be produced.

Further, one or more than two of acidifier such as citric acid, tartaric acid, and malic acid, a foaming agent such as baking soda, an artificial sweetener such as dipotassium glycyrrhizinate, aspartame, stevia, and thaumatin, a perfume such as lemon, lemon lime, orange, and menthol, a coloring agent such as food yellow No.5, food red No.2, food blue No.2 may be

added if required in the procedure of producing a mixed powder (particle) 5b.

Fig.8 is an explanatory view diagrammatically showing how the tablet Tb (intrabuccally rapidly disintegrable tablet) is disintegrated in oral cavity. Fig.8(a) is a perspective view of the intrabuccally rapidly disintegrable tablet Tb, Fig.8(b) is a diagrammatic view in which the area R3 in Fig.8(a) is enlarged, Fig.8(c) is a diagrammatic view in which the area R4 in Fig.8(b) is enlarged, and Fig.8(d) is a diagrammatic view showing how the tablet Tb (intrabuccally rapidly disintegrable tablet) is disintegrated in saliva.

According to this tablet Tb (intrabuccally rapidly disintegrable tablet), binding between the particles 2 ···, 3 ···, 4 ···, 9 ··· of the granulated material 1b included in the tablet Tb is achieved by the water-soluble polymer 7.

Therefore, when the tablet Tb doesn't touch water, the particles 2 ···, 3 ···, 4 ···, 9 ··· are bound by a water soluble polymer 7 so that each granulated material 1b is hardly broken like a normal tablet. Thereby, the tablet Tb is hardly chipped while storage and transportation.

Further, as a saccharide particle with high moldability 9 ··· is included in the granulated material 1b, tabletting problems such as sticking, laminating, and capping aren't caused for the produced tablet Tb in the process of compressing and tabletting granulated material 1b.

On the other hand as shown in Fig.8(d), when the tablet Tb is given in oral cavity, the particle (precipitation of fine particle) 8 ··· of saccharide with high wettability against water is dispersed in a binder 6 like the tablet Ta. Accordingly, the tablet Tb (intrabuccally rapidly disintegrable tablet) is rapidly disintegrated in oral cavity by means of the same action as the tablet Ta.

Further, when the particle 3 of saccharide with high wettability against water and the particle (precipitation of fine particle) 8 ··· of saccharide with high wettability against water are dissolved in saliva, they don't make the viscosity of saliva η in which they are dissolved high comparing with the viscosity of water η w. Thereby, when the particle 3 of saccharide with high wettability against water and the particle (precipitation of fine particle) 8 ··· of saccharide with high wettability against water are dissolved in saliva, the viscosity

of saliva doesn't become high so that saliva is quickly permeated in the tablet Tb. The tablet Tb is rapidly disintegrated in oral cavity also because of such function.

(Embodiment of the Invention 3)

Fig.9 is an explanatory view diagrammatically showing another preferable embodiment of a granulated material used in the intrabuccally rapidly disintegrable tablet of the present invention.

A granulated material 1c is constructed the same as the granulated material 1b shown in Fig.5 excluding the following constructions so that the corresponding particle is allotted with corresponding reference numeral and their explanations are omitted.

The granulated material 1c is different from the granulated material 1b in the construction of a binder 6c for binding a mixed powder (particle) 5b including a principal agent (particle) 2, the particle 3 of saccharide with high wettability against water, a disintegrant particle 4, and the saccharide particle with high moldability 9.

The granulated material 1c is comprised such that the particle 2 ···, 3 ···, 4 ···, 9 ··· comprising the mixed powder (particle) 5b is bound by a binder 6c wherein the particle (precipitation of fine particle) 8 ··· of saccharide with high wettability against water and a surface active agent 10 ··· are dispersed in a water-soluble molecular 7.

Anionic surface-active agents, cationic surfactant, nonionic surfactant, amphoteric surfactant may be used as a surface active agent, or high molecular surface active agent such as Pluron or Poloxamer may be used.

More concretely, preferable example of anionic surface-active agents is sulfates ($R\cdot O\cdot SO_3^-\cdot M^+$) such as sodium lauryl sulfate.

Preferable example of nonionic surfactant is sorbitan esters and polysorbates, of which preferable example is polysorbate 80.

A surface active agent of which HLB (hydrophile-lipophile balance) is greater than or equal to 10 and less than or equal to 40 is preferable. Such surface active agent includes polyoxyethylene (20) sorbitan monooleate) (HLB=15.0), Polyoxy-ethylene (20) sorbitan monopalmitate) (HLB=15.6),

Polyoxyethylene (20) sorbitan monolaurate (HLB=16.7), Polyoxyethylene (30) sorbitan stearate (HLB=16.0), Polyoxyethylene (40) stearate (HLB=16.9), Polyoxyethylene (100) stearate (HLB=18.8), triethanol-amine oleate (HLB=12.0), Sodium oleate (HLB=18.0), and sodium lauryl sulfate (HLB=40).

The ratio of the surface active agent 10 to a water-soluble polymer is defined by experiments considering the strength of binder 6c and the wettability of binder 6c for saliva (namely water).

Fig.10 and Fig.11 are process drawings schematically showing another embodiment of production procedure of the intrabuccally rapidly disintegrable tablet of the present invention.

The production method is the same as the production method of the tablet (intrabuccally rapidly disintegrable tablet) Tb as shown in Fig.6 and Fig.7.

More specifically according to the production method, a mixed powder (particle) 5b is prepared by homogeneously mixing a principal agent (particle) 2 ···, the particle 3 of saccharide with high wettability against water, a disintegrant (particle) 4 ···, and the saccharide particle with high moldability 9 ··· by a mixer.

Then an aqueous solution in which appropriate amount of surface active agent is dissolved other than a water-soluble polymer and a saccharide with high wettability against water is prepared for granulating the mixed powder 5b in the process in Fig.10(b).

As shown in Fig.10(c), an aqueous solution in which a water-soluble polymer, a saccharide with high wettability against water, and a surface active agent are dissolved which are adjusted in the procedure Fig.10(b) is sprayed from a spraying means 12 in order to granulate the mixed powder (particle) 5b.

Then, in the procedure shown in Fig.11(a), thus produced granulated material 1c ··· in the process in Fig.10(c) is compressed and molded and the tablet Tc (intrabuccally rapidly disintegrable tablet) is produced (See Fig.11(b)).

Fig.12 is an explanatory view diagrammatically showing how the tablet Tc (intrabuccally rapidly disintegrable tablet) is disintegrated in oral cavity. Fig.12(a) is a perspective view of the intrabuccally rapidly disintegrable tablet Tc, Fig.12(b)

is a diagrammatic view in which the area R5 in Fig.12(a) is enlarged, Fig.12(c) is a diagrammatic view in which the area R6 in Fig.12(b) is enlarged, and Fig.12(d) is a diagrammatic view showing how the tablet Tc (intrabuccally rapidly disintegrable tablet) is disintegrated in saliva.

According to this tablet Tc (intrabuccally rapidly disintegrable tablet), binding between the particles 2 ···, 3 ···, 4 ···, 9 ··· of the granulated material 1c included in the tablet Tc is achieved by a water-soluble polymer 7 like the tablet Ta and Tb as shown in Fig.12(b) and Fig.12(c).

Therefore, when the tablet Tc doesn't touch water, the particles 2 ···, 3 ···, 4 ···, 9 ··· are bound by a water soluble polymer 7 so that each granulated material 1c ··· is hardly broken like a normal tablet. Thereby, the tablet Tc is hardly chipped while storage and transportation.

Further, as a saccharide particle with high moldability 9 ··· is included in a granulated material 1c, tabletting problems such as sticking, laminating, and capping aren't caused for the produced tablet Tc in the process of compressing and tabletting the granulated material 1c.

On the other hand as shown in Fig.12(d), when the tablet Tc is given in oral cavity, the tablet Tc (intrabuccally rapidly disintegrable tablet) is rapidly disintegrated in oral cavity by means of the same action as the tablet Ta, Tb because the particle (precipitation of fine particle) 8 ··· of saccharide with high wettability against water is dispersed in a binder 6 like the tablet Ta, Tb.

Further, when the particle 3 ··· of saccharide with high wettability against water and the particle (precipitation of fine particle) 8 ··· of saccharide with high wettability against water are dissolved in saliva, they doesn't make the viscosity of saliva η in which they are dissolved high comparing with the viscosity of water ηw. Thereby, when the particle 3 ··· of saccharide with high wettability against water and the particle (precipitation of fine particle) 8 ··· of saccharide with high wettability against water are dissolved in saliva, the viscosity of saliva doesn't become high so that saliva is quickly permeated in the tablet Tc. The tablet Tc is rapidly disintegrated in oral cavity also because of such function.

Further, according to the tablet Tc, the particle 2 ···, 3 ···, 4 ···, 9 ··· are bound by a binder 6c including surface active

agent 10 ··· other than the particle (precipitation of fine particle) 8 ··· of saccharide with high wettability against water.

Therefore, when the tablet Tc is given in oral cavity, a binder 6c is easily wettable in water because the surface active agent 10 contained in the binder 6c makes the surface tension of water contained in saliva lower. Then the particle (precipitation of fine particle) 8 ··· of saccharide with high wettability against water gets wet and is dissolved or dispersed in saliva from the binder 6c. Therefore, the binding force between the particle 2 ···, 3 ···, 4 ···, 9 ··· in the binder 6c is lost, thereby granulated material 1c is rapidly disintegrated.

Here, the granulated material 1c wherein the mixed powder 5b including a principal agent (particle) 2, the particle 3 of saccharide with high wettability against water, a disintegrant particle 4, and the saccharide particle with high moldability 9 is bound by a binder 6c including the particle (precipitation of fine particle) 8 ··· of saccharide with high wettability against water and a surface active agent 10 ··· is explained. However, the mixed powder 5a including a principal agent (particle) 2, the particle 3 of saccharide with high wettability against water, and a disintegrant particle 4 may be bound by a binder 6c including the particle (precipitation of fine particle) 8 ··· of saccharide with high wettability against water and a surface active agent 10 ··· and thus granulated material may be compressed to produce a tablet (intrabuccally rapidly disintegrable tablet).

Next, the present invention is explained based on a practical experimental data.

An embodiment for producing a placebo tablet is explained in order to facilitate explanation in the following experiments.

(Example producing a tablet by an internal lubricating method)

Mannitol powder (Japanese Pharmacopoeia) and lactose powder (Japanese Pharmacopoeia) were prepared and were filtered with a fixed coarse mesh, then a granular material with a desired particle diameter and particle distribution was produced.

Next, mannitol powder with a desired particle diameter and particle distribution and lactose powder with a desired particle diameter and particle distribution were combined in such a

manner that the volume ratio of mannitol powder and lactose powder was 7 : 3. Appropriate amount of disintegrant was added (povidone was used so as to be 5 volume% of entire volume in this embodiment) and they were homogeneously mixed by means of a mixer to produce a mixed powder (particle).

A binder solution used for granulation is prepared wherein polyvinyl alcohol (PVA) is adjusted to be 1 volume% and mannnitol is adjusted to be 5 volume %.

Next, the mixed powder (particle) in which mannitol powder, lactose powder, and disintegrant were homogeneously mixed was stored in a granulation tank of a fluid-layer granulation means and was blended with a heated air to be fluidized layer. The binder solution which was adjusted to include 1 volume% of polyvinyl alcohol (PVA) and 5 volume% of mannitol was sprayed to the mixed powder by a spay provided in the granulation tank. Then it was dried to produce a granulated material with average particle diameter of 250μm.

Then 0.5 weight% of magnesium stearate was combined as a lubricant in the granulated material, and the granulated material was tabletted with an upper punch of 7mm diameter and a lower punch of 7mm diameter at a tabletting pressure of 133kg/punch by means of the rotary tabletting machine (Hata Tekkosho Co., Ltd.), then a tablet (intrabuccally rapidly disintegrable tablet) of which weight was 100mg, diameter was 7mm and thickness was 2.5mm was produced.

The hardness of the tablet was 3.9kg in average (the number of measured tablet n=3).

The disintegration time of the tablet in water was 15 seconds (the number of measured tablet n=3).

Tabletting troubles (sticking, laminating, and capping) caused for the produced tablet in case of continuous tabletting were observed, however such troubles weren't found.

(Example producing a tablet by an external lubricant spraying method)

Mannitol powder (Japanese Pharmacopoeia) and lactose powder (Japanese Pharmacopoeia) were prepared and were filtered with a fixed coarse mesh, then a granular material with a desired particle diameter and particle distribution was produced.

Next, mannitol powder with a desired particle diameter and particle distribution and lactose powder with a desired particle diameter and particle distribution were combined in such a

manner that the volume ratio of mannitol powder and lactose powder was 7 : 3. Appropriate amount of disintegrant was added (povidone was used so as to be 5 volume% of the entire volume in this embodiment) and they were homogeneously mixed by means of a mixer to produce a mixed powder (particle).

The binder solution used for granulation was prepared wherein polyvinyl alcohol (PVA) was adjusted to be 1 volume% and mannnitol was adjusted to be 5 volume%.

Next, the granulated material was tabletted by means of the external lubricant spraying method as shown in Fig.13 - Fig.22 without adding a lubricant.

Then the granulated material was tabletted with an upper punch of 7mm diameter and a lower punch of 7mm diameter at a tabletting pressure of 133kg/punch by means of the rotary tabletting machine (Hata Tekkosho Co., Ltd.), then a tablet (intrabuccally rapidly disintegrable tablet) of which weight was 100mg, diameter was 7mm and thickness was 2.5mm was produced.

The hardness of the tablet was 5.7kg in average. It was found that the hardness was increased about 30% comparing with the tablet produced by the internal lubricating method (the number of measured tablet n=3).

The disintegration time of the tablet in water was 11 seconds in average and it was found that the disintegration time was about 25% shorter than the tablet produced by the internal lubricating method (the number of measured tablet n=3).

Tabletting troubles (sticking, laminating, and capping) caused for the produced tablet in case of continuous tabletting were observed, however such troubles weren't found.

From the above-mentioned results, it was found that the tablet produced by an external lubricant spraying method had higher hardness and a quick disintegration time than the tablet produced by an internal lubricating method.

Then, the construction of the external lubricant spraying type tabletting machine 51 and its production method used in this experiment are explained hereafter.

(Explanation of an external lubricant spraying type tabletting machine used for producing the tablet of the present invention)

Fig.13 shows a diagrammatic entire construction of an external lubricant spraying type tabletting machine used for producing the tablet of the present invention.

The external lubricant spraying type tabletting machine 51 is comprised of a pulsating vibration air generation means 61 for generating positive pulsating vibration air, a discharge means (quantitative feeder) 71 for mixing and dispersing a lubricant (powder) in the positive pulsating vibration air generated from the pulsating vibration air generation means 61, a rotary type tabletting machine 81, a lubricant spray means 91, a suction means 101, and a control means 111 provided for controlling and managing the entire external lubricant spraying type tabletting means 51.

The rotary type tabletting machine 81 is provided with a rotary table 85 having plural dies 84 ···, plural upper punches 82 ···, and plural lower punches 83 ···.

The lubricant spray means 91 is fixedly positioned above the rotary table 85 of the rotary tabletting machine 81 and is provided for spraying a lubricant on each surface (lower surface) of the upper punches 82 ···, each surface (upper surface) of the lower punches 83 ···, and each surface (inner circumference) of the dies 84 ··· of the rotary-type tabletting machine 81.

The suction means 101 is provided for discharging extra lubricant sprayed in the lubricant praying means 91.

The pulsating vibration air generation means 61 is provided with an air source 62 such as a blower and a pulsating vibration air conversion means 63 for converting compressed air generated by the air source 62 to pulsating vibration air.

In this embodiment, the air source 62 is connected with the pulsating vibration air generation means 63 via a conduit C3.

Further, a flow rate control means 64 for controlling the pressure and the flow amount of compressed air generated by the air source 62 into a fixed pressure and flow amount is provided in midstream of the conduit C3.

In this embodiment, an open-close valve such as an electromagnetic valve for opening and closing the conduit C3 is used as the flow rate control means 64.

In Fig.13 the member shown as 65 is a driving means such as a motor for driving a rotary cam (refer to a rotary cam 67 in Fig.15) comprising a rotary cam mechanism (refer to a rotary cam mechanism 66 in Fig.15) for producing pulsating vibration air of the pulsating vibration air conversion means 63.

In the external lubricant spraying type tabletting machine

51, the pulsating vibration air generation means 61 and the lubricant spraying means 91 are connected by the conduit C1.

The discharge means (quantitative feeder) 71 is connected in midstream of the conduit C1.

More detailed, the pulsating vibration air conversion means 63 of the pulsating vibration air generation means 61 is connected to the quantitative feeder 71 via a conduit C1a.

Further, the quantitative feeder 71 is connected to the lubricant spraying means 91 via a conduit C1b.

According to the above-mentioned construction, the positive pulsating vibration air generated by driving the pulsating vibration air generation means 61 is supplied to the lubricant spraying means 91 via the conduit C1 (conduit C1a, C1b).

Then a fixed amount of lubricant L is supplied from the discharge means (quantitative feeder) 71 to the positive pulsating vibration air flowing from the pulsating vibration air generation means 61 to the lubricant spraying means 91 in the conduit C1b so that the lubricant L is mixed and dispersed in the positive pulsating vibration air.

Thus, the lubricant L mixed and dispersed in the positive pulsating vibration air is supplied to the lubricant spraying means 91 and is sprayed on the surface of the upper punch 82, lower punch 83 and the die 84 contained in the lubricant spraying means 91.

For facilitating explanation, the conduit connecting the pulsating vibration air generation means 61 and the discharge means (quantitative feeder) 71 is called as C1a and the conduit connecting the discharge means (quantitative feeder) 71 and the lubricant spraying means 91 is called as C1b hereinafter.

The suction means 101 such as a blower is connected to the lubricant spraying means 91 via the conduit C2 and the extra lubricant among the lubricant L supplied in the lubricant spraying means 91 is suck to be removed from the lubricant spraying means 91.

The control means 111 is connected to the pulsating vibration air generation means 61 via a signal line L1 in such a manner that signals can be sent and received between the control means 111 and the pulsating vibration air generation means 61. The pulsating vibration air generation means 61 is designed to be operated following the command of the control means 111.

Particularly, the signal line L1 introduced from the control

means 111 is diverged into two signal lines L1a, L1b. The signal line L1a is connected to the flow rate control means 64 and the signal line L1b is connected to the driving means 65 of the pulsating vibration air conversion means 63. According to such construction, when a command is delivered to the flow rate control means 64 from the control means 111, the flow rate control means 64 is designed to control the conduit C3 at a fixed opening degree. Further, when the command is delivered to the driving means 65 from the control means 111, the driving means 65 is designed to rotate the rotary cam 67 at a fixed rotary speed.

The control means 111 is connected to the suction means 101 via the signal line L2 so that the signals can be sent and received between the control means 111 and the pulsating vibration air generation means 61 and the pulsating vibration air generation means 61 is designed to be operated by the command from the control means 111. According to such construction, when a command is delivered to the suction means 101 from the control means 111, the suction means 101 is designed to be controlled at a fixed suction amount.

A light scattering type powder density measuring means 112 is provided in midstream of the conduit C2.

Particularly, the powder density measuring means 112 in this embodiment is provided with a laser beam irradiation equipment (not shown) for exposing a laser beam and a light receiving means (not shown).

The laser beam irradiation equipment (not shown) and the light receiving means (not shown) are opposed so as to sandwich a measuring member (not shown) provided at the conduit C2.

The measuring member (not shown) is made of a clear material such as glass or acrylate resin in order that the scattering light scattered by the particle of the lubricant L passing through the measuring member (not shown) is received in the light receiving means when laser beam is exposed from the laser beam irradiation equipment (not shown) to the measuring member (not shown).

The information received in the light receiving means (not shown) is sent to the control means 111 and the density of the lubricant L flowing in the measuring member (not shown) is calculated according to the density analysis program based on the well-known Mie Scatter Theory which is stored in a memory of the control means 111 in advance. Then the calculated result

is shown on a display (not shown) of the control means 111.

Herewith, an operator can control spraying amount of the lubricant (powder) L sprayed from the lubricant spraying means 91 by controlling driving amount of the suction means 101.

Next, construction and operation of the external lubricant spraying type tabletting machine 51 are explained in more detail having an eye to the rotary type tabletting machine.

Fig.14 is a plane view of a rotary-type tabletting machine 81 of the external lubricant spraying type tabletting machine 51 in Fig.13.

The rotary tabletting machine 81 is provided with a rotary table 85, plural upper punches 82···, and plural lower punches 83 ···.

Plural dies 84 ··· are formed along the circumference of the rotary table 85.

Each of the plural upper punches 82 ··· is provided so as to correspond to each of the plural dies 84 ··· formed on the rotary table 85. When the rotary table 85 is rotated at a fixed rotary speed, each upper punch 82 ··· is rotated at a fixed speed so as to synchronize with each corresponding die 84 ···.

Each lower punch 83 ··· is provided so as to correspond with each die 84 ··· provided for the rotary table 85 and is rotated at a fixed speed so as to synchronize with each corresponding die 84 ··· when the rotary table 85 is rotated at a fixed speed.

The numeral 86 shows a rotary cam mechanism for lower punches for executing rotary movement and vertical movement of plural lower punches 83 ···. Practically each of plural upper punches 82 ··· is also designed to execute rotary and vertical movements by a rotary cam mechanism for upper punches like the rotary cam mechanism for lower punches. However, the rotary cam mechanism for upper punches isn't shown for easy understanding in the figure.

According to the rotary tabletting machine 81, lubricant L is designed to be homogeneously applied on each surface (inner circumference) of the dies 84 ···, each surface (lower surface) of the upper punches 82 ··· and each surface (upper surface) of the lower punches 83 ··· at a lubricant spray position P1 as shown in Fig.14.

More practically, a lubricant spray means 91 is provided above the lubricant spray position P1 of the rotary table 85. Lubricant L is homogeneously applied on the surface (inner

circumference) of the die 84 above the upper surface of the lower punch 83 inserted in a fixed position in the die 84 when the die 84 is positioned in the lubricant spraying means 91, the surface (upper surface) of the lower punch 83 and the surface (lower surface) of the upper punch 82 according to rotation of the rotary table 85 while they are contained in the lubricant spray means 91.

The die 84 on which surface (inner circumference) lubricant L is applied, the upper punch 82 on which surface (lower surface) lubricant L is applied, and the lower punch 83 on which surface (upper surface) lubricant L is applied by the lubricant spray means 91 at the lubricant spray position P1 are sent to molding material charge point P2 and molding material is charged in a space formed by the surface (upper surface) of the lower punch 83 inserted at a fixed position in the die 84 and the surface (inner circumference) of the die 84.

In more detail, a molding material charge means (feed chute) 121 is fixedly provided above the molding material charge position P2 of the rotary table 85.

A molding material storage hopper (not shown) for storing molding material m is connected to the molding material charge means (feed chute) 121 via a material feed valve (not shown). Molding material m stored in the molding material storage hopper (not shown) is supplied or not supplied into the molding material charge means (feed chute) 121 by opening and closing the material feed valve (not shown).

When the material feed valve (not shown) is opened, molding material fed in the molding material charge means (feed chute) 121 is supplied from a zigzag groove of the molding material charge means (feed chute) 121 to the space formed by the die 84 and the lower punch 83 inserted at a fixed position in the die 84.

Extra molding material of the molding material m supplied in the space formed by the die 84 and the lower punch 83 inserted at a fixed position in the die 84 is scraped and removed by a scraper 122 provided at a terminal end of the molding material charge means (feed chute) 121.

Following the above-mentioned procedures, the molding material m charged in the space formed by the die 84 and the upper surface of the lower punch 83 inserted at a fixed position in the die 84 is previously compressed with the upper punch 82

and the lower punch 83 corresponding to the die 84 at a pre-compression point P3, then is compressed to produce a tablet t with the upper punch 82 and the lower punch 83 corresponding to the die 84 at an actual compression point P4.

When the die 84 comes to a material discharge point P5, the lower punch 83 inserted in the die 84 is raised to the upper end of the die 84, then the tablet produced in the die 84 is discharged at a fixed position by a tablet discharge arm 131 fixedly provided at the tablet discharge position P5 above the rotary table 85.

The position P6 in Fig.14 shows cleaning position for cleaning each surface of the upper punch 82 ···, the lower punch 83 ···, and the die 84 ···. An upper punch cleaning means (not shown), a lower punch cleaning means (not shown), and a die cleaning means (not shown) are provided at the cleaning position P6.

Next, construction and operation of the pulsating vibration air generation means 61 used for the external lubricant spraying type tabletting machine 51 are explained in more detail.

Fig.15 is an explanatory view of the pulsating vibration air generation means 61.

As mentioned above, the pulsating vibration air generation means 61 is provided with the air source 62 and the pulsating vibration air conversion means 63 connected to the air source 62 via the conduit C3. The flow rate control means 64 is provided in midstream of the conduit C3.

The pulsating vibration air generation means 63 is provided with a valve chamber R having a valve seat 68 between an input port 68a and an output port 68b, a valve plug 69 capable of opening and closing the valve seat 68, a cam mechanism for vertically moving the valve plug 69, and a case body 70 for containing the cam mechanism 66.

A penetrating hole 68h narrowing into the direction of the output port 68b is formed in the valve seat 68.

The valve plug 69 is narrowed like a cone so as to meet the shape of the penetrating hole 68h of the valve seat 68 so that the valve plug 69 can close the valve seat airtightly.

The valve plug 69 has an axis 69a which is contained in an axis hole 70h provided in a case body 70 airtightly and movable vertically.

A roller 69b is rotatably attached at the lower end of the

axis 69a.

The cam mechanism 66 has a rotary cam 67 rotatably provided by means of a driving means such as a motor (a driving means 65 in Fig.13) and the roller 69b rotatably attached at the lower end of the axis 69a of the valve plug 69 is rotatably held for the rotary cam 67.

Concavo-convex patterns p1, p2 are provided on the rotary cam 67.

More practically, the rotary cam 67 has an inner rotary cam 67a and an outer rotary cam 67b. The concavo-convex pattern p1 of the inner rotary cam 67a and the concavo-convex pattern p2 of the outer rotary cam 67b are aligned each other so as to have a space of the diameter of the roller 69b or a little larger space.

The roller 69b is rotatably held between the inner rotary cam 67a and the outer rotary cam 67b. When the rotary cam 67 is rotated, the roller 69b accurately moves up and down according to the concavo-convex pattern p1 of the inner rotary cam 67a and the concavo-convex pattern p2 of the outer rotary cam 67b.

Accordingly, as the valve plug 69 accurately moves up and down according to the concavo-convex pattern p1 of the inner rotary cam 67a and the concavo-convex pattern p2 of the outer rotary cam 67b, the rotary plug 69 can open and close the penetrating hole 68h of the valve seat 68 according to the concavo-convex pattern p1 of the inner rotary cam 67a and the concavo-convex pattern p2 of the outer rotary cam 67b.

The input port 68a is connected to the air source 62 such as a blower via the conduit C3.

In this embodiment, an example having the flow rate control means 64 in midstream of the conduit C3 is explained, however, the flow rate control means 64 isn't always required.

The conduit C1 (more practically the conduit C1a) is connected to the output port 68b.

In Fig.15 the numeral 68c shows a flow rate control port.

An output control valve v is provided for the flow rate control port 68c.

The output control valve v is designed to adjust the flow rate control port 68c at a desired condition till completely closed condition from completely communicated condition with outer air.

The output control valve v isn't limited if it can adjust

opening rate of the flow rate control port 68c at a desired rate and well known switch valve such as an electromagnetic valve may be used. However in the present invention, the flow rate control port 68c and the output control valve v aren't always necessary.

Next, a supply method of pulsating vibration air in the conduit C1 (more practically the conduit C1a) by means of the pulsating vibration air generation means 61 is explained hereinafter.

The rotary cam 67 having the concavo-convex patterns p1, p2 which can generate pulsating vibration air having wave shape suitable for easily mixing lubricant is selected based on the particle diameter, particle distribution, and physical property of the lubricant particle contained in the storage hopper (the storage hopper 72 in Fig.13 and Fig.16) of the discharge means (quantitative feeder) 71.

Next, thus selected rotary cam 67 is attached on a rotary axis 65a of the drive means (drive means 65 in Fig.13) for rotating the driving cam 67.

Then, if the flow rate control means 64 is provided, it is appropriately controlled.

If the output control valve v is provided, it is appropriately controlled.

The drive means (drive means 65 in Fig.13) is driven to rotate the rotary axis 65a at a fixed speed so that the rotary cam 67 is rotated at a fixed speed.

The air source 62 is driven and compressed air with almost constant air pressure and fixed flow amount is supplied in the conduit C3.

The compressed air supplied in the conduit C3 is adjusted into desired pressure and desired flow amount if the flow rate control means 64 is provided, then supplied to the valve chamber R.

The compressed air supplied in the valve chamber R is converted to pulsating vibration air by the rotary cam mechanism 66 provided in the casing 70 and is discharged to the conduit C1 from the output port 68b.

When the rotary cam 67 is rotated at a fixed speed, the valve plug 69 is moved up and down according to the concavo-convex patterns p1, p2 of the rotary cam 67. Thereby, the penetrating hole 68h of the valve seat 68 is controlled to be opened and

closed by the valve plug 69 vertically moved by the concavo-convex patterns P1, p2 of the rotary cam 67, for example, full open, half open, and full closed.

Herewith pulsating vibration air is discharged from the output port 68 to the conduit C1.

The pulsating vibration generated from the pulsating vibration air generation means 61 is clearly different from the intermittent air generated by opening and closing a wave transmission pipe 4 in such a manner that a switching means such as an electromagnetic valve is provided for opening and closing the conduit C1 or the conduit C3 instead of the pulsating vibration air conversion means 63 in midstream of the conduit C1 or C3 connecting the air source 62 and the lubricant spray means 91.

This is explained hereinafter in more detail.

When a switching means such as an electromagnetic valve is provided for opening and closing the conduit C1 or the conduit C3 in midstream of the conduit C1 or C3 connecting the air source 62 and the lubricant spray means 91, intermittent air is simply fed in the conduit C1.

By the way, when the rotary cam 67 is rotated, the valve pplug 69 is vertically moving up and down according to the concave-convex patterns p1 p2 of the rotary cam 67. Hence the penetrating hole 68h of the valve seat 68 is controlled to be opened and closed by the valve plug 69 vertically moving according to the concavo-convex patterns p1, p2 of the rotary cam 67. Therefore, pulsating vibration air having wave shape according to the concavo-convex pattern p1, p2 of the rotary cam 67 can be fed to the conduit C1.

When the drive amount control and flow rate control means 64 of the air source 62 is provided and adjustment and output control valve v of the flow rate control means 64 is provided, several kinds of pulsating vibration air having different frequency, amplitude, and wave shape can be generated in the conduit C1 by executing control of the output control valve v, control of rotary speed of the rotary cam 67, and exchange of the rotary cam 67 solely or in combination.

By such control, pulsating vibration air with a fixed frequency (period) and the peak and valley of which amplitude are positive and pulsating vibration air with a fixed frequency (period), the peak of which amplitude is positive and the valley

of which amplitude is almost atmosphere can be produced.

Next construction and operation of the discharge means (quantitative feeder) 71 used for the external lubricant spraying type tabletting machine 51 are detailed hereinafter.

Fig.16 is a diagrammatic sectional view of discharge means (quantitative feeder) 71.

The discharge means (quantitative feeder) 71 has the storage hopper 72, a cylindrical body 74 airtightly attached under a material discharge port 72a of the storage hopper 72, an elastic membrane 73 provided so as to close the bottom of the cylindrical body 74, and a dispersion chamber 75 connected to the material discharge port 72a of the storage hopper 72 via the elastic membrane 73.

The storage hopper 72 is provided so as to contain lubricant (powder) L.

Fig.17 is a plane view diagrammatically showing the elastic membrane.

An aperture (slit) 73s with a fixed length is provided at the center of the elastic membrane 73 so as to penetrate the membrane 73 as shown in Fig.17.

In this embodiment, a fixed amount of lubricant L is always stored on the elastic membrane 73.

It is explained in more detail hereinafter.

The cylindrical body 74 is airtightly connected to the discharge port 72a of the storage hopper 72 as mentioned and the elastic membrane is provided so as to construct the bottom of the cylindrical body 74.

A material feed valve 77 for opening and closing the material discharge port 72a of the storage hopper 72 is provided at an upper cylindrical body 74a of the cylindrical body 74.

In this embodiment, a lower cylindrical body 74b of the cylindrical body 74 is made of clear material such as polycarbonate, acrylate resin, or glass. A level sensor 76 is provided at a fixed height H of the lower cylindrical body 74b above where the elastic membrane 73 is provided.

Each material feed valve 75 and level sensor 76 is connected to the control means (control means 111 in Fig.13) via a signal line (not shown) so that the material feed valve 75 opens or closes the material discharge port 72a of the storage hopper 72 based on the signals detected by the level sensor 76.

This embodiment uses a level sensor 76 which has a light

emitting element 76a and a light receiving element 76b.

Each light emitting element 76a and light receiving element 76b is designed to be attached on a support shaft P, P capable of adjusting its height.

The light emitting element 76a can emit visible light such as red light or light such as infra-red radiation (hereinafter only called as "light").

The light emitting element 76a and the light receiving element 76b are opposed so as to sandwich the lower cylindrical body 74b of the cylindrical body 74 and light emitted from the light emitting element 76a passes through the lower body 74b and is received at the light receiving element 76b.

According to such constructed discharge means (quantitative feeder) 71, when the amount of lubricant L on the elastic membrane 73 is lower than the height H, light emitted from the light emitting element 76a is received at the light receiving element 76b. However, when the amount of lubricant L on the elastic membrane 73 becomes the height H, light emitted from the light emitting element 76a is blocked by the lubricant L so that the height H of the lubricant L on the elastic membrane 73, namely the amount of lubricant L on the membrane 73, can be detected.

According to this discharge means (quantitative feeder) 71, the control means 111 controls such that the material feed valve 77 is opened when the light receiving element 76b of the level sensor 76 receives light emitted from the light emitting element 76a and the material feed valve 77 is closed when the light receiving element 76b doesn't receive light emitted from the light emitting element 76a. Therefore, the amount of lubricant L on the elastic membrane 73 can be always kept at the height H above the elastic membrane 73.

If a level sensor 76 of which light emitting element 76a emits visible light such as red light is used, it is preferable that the lower cylindrical body 74b of the cylindrical body 74 is made of clear material having high translucency. Further, it is preferable that the lower cylindrical body 74b is made of such material that lubricant L hardly attaches on the inner circumferential wall of the body 74b in order to accurately measure the amount of lubricant L in the body 74b. Considering this, it is preferable that the lower cylindrical body 74b is made of polycarbonate and its inner circumferential wall is mirror finish.

The dispersion chamber 75 is airtightly connected under the material discharge port 72a of the storage hopper 72 via the elastic membrane 73 as shown in Fig.16.

The dispersion chamber 75 is formed like a cylindrical tube, an introduction port 75a of the pulsating vibration air is provided at the lower part of the chamber 75, and a discharge port 75b of pulsating vibration air is provided above the introduction port 75a.

In this embodiment, the introduction port 75a is so installed at the dispersion chamber as to be parallel to a tangent of the inner circumference of the dispersion chamber 75. The discharge port 75b is also so installed at the dispersion chamber 75 so as to be parallel to the tangent of the inner circumference of the dispersion chamber 75. Further, the introduction port 75a and the discharge port 75b are positioned so as not to oppose each other.

The conduit C1a is connected to the introduction port 75a and pulsating vibration air generated by the pulsating vibration air generation means 61 is supplied in the dispersion chamber 75 from the introduction port 75a.

The conduit (the conduit C1b in Fig.13) is connected to the discharge port 75b and pulsating vibration air supplied in the dispersion chamber 75 from the introduction port 75a is supplied to the conduit C1b.

By the way, in this embodiment as mentioned above, the introduction port 75a is provided at the lower part of the chamber 75 at tangential adjusting on the inner circumference in the dispersion chamber 75. And the discharge port 75b is provided at the upper part of the chamber 75 at tangential adjusting on the inner circumference in the dispersion chamber 75.

By such construction, pulsating vibration air supplied in the dispersion chamber 75 from the introduction port 75a becomes swirling flow of pulsating vibration air from bottom to top toward the discharge port 75b from the introduction port 75a in the dispersion chamber 75 so that pulsating vibration air is discharged out of the dispersion chamber 75.

The pulsating vibration air swirling in the dispersion chamber 75 doesn't lose its feature.

Then operation of the discharge means (quantitative feeder) 71 is explained.

Lubricant L is contained in the storage hopper 72 at first

when the discharge means (quantitative hopper) 71 is operated.

Then, the control means 111 is turned on.

Light is emitted from the light emitting element 76a of the level sensor 76.

While the light is received in the light receiving element 76b, the material feed valve 75 is opened, the lubricant L stored in the storage hopper 72 falls in the cylindrical body 74 to be accumulated on the elastic membrane 73.

At the time when the amount of lubricant L accumulated on the elastic membrane 73 becomes the height H above the elastic membrane 73, the light emitted from the light emitting element 76a is blocked by the lubricant L accumulated on the elastic membrane 73. When the light receiving element 76b doesn't receive the light such as red light or infra-red radiation emitted from the light emitting element 76a, the material feed valve 75 is closed.

Thereby, the amount of the lubricant L on the elastic membrane 73 is kept at the height H above the membrane 73.

While the discharge means (quantitative feeder) 71 is operated, the light emitting element 76a of the level sensor 76 is always turned on.

Therefore, the amount of the lubricant L on the elastic membrane 73 is kept at the height H above the elastic membrane while operating the discharge means (quantitative feeder) 71.

Then, the pulsating vibration air generation means 61 is driven and generated pulsating vibration air is supplied in the conduit C1a.

Pulsating vibration air supplied in the conduit C1a transfers in the conduit C1a and is supplied in the dispersion chamber 75 from the introduction port 75a thereof.

Fig.18 is a view explaining operation of the elastic membrane 73 comprising the discharge means (quantitative feeder) 71.

As mentioned above, the pulsating vibration air swirling in the dispersion chamber 75 doesn't lose its feature. Therefore, when the amplitude of the pulsating vibration air is peak, the pressure in the dispersion chamber 75 is heightened because of the property of the pulsating vibration air so that the elastic membrane 73 is elastically deformed and its center is curved upward as shown in Fig.18(a).

In this time, the aperture (slit) 73s is shaped like a letter

V of which upper part is opened as shown in Fig.18(a) and a part of lubricant L on the elastic membrane 73 in the cylindrical body 74 falls in the V-shaped aperture (slit) 73s.

When pulsating vibration air supplied in the dispersion chamber 75 changes into valley from the peak and the pressure in the chamber 75 is lowered, the elastic membrane 73 curved upward is elastically deformed so as to be returned to its original shape because of resilience as shown in Fig.18(b).

Because the V-shaped aperture (slit) 73s is going to return its original closed condition, the lubricant L fallen in the aperture (slit) 73s is sandwiched therein.

Then the amplitude of pulsating vibration air supplied in the dispersion chamber 75 changes to its valley and the pressure in the dispersion chamber 75 is further lowered, the elastic membrane 73 at its original condition is elastically deformed corresponding to its resilience force and/or lowering of the pressure in the dispersion chamber 75 so that its center is curved downward as shown in Fig.18(c).

The aperture (slit) 73s is formed like a reversed letter V of which bottom is opened as shown in Fig.18(c) and the lubricant L sandwiched in the aperture (slit) 73s falls in the dispersion chamber 75 so that the lubricant L is mixed with pulsating vibration air swirling and dispersed in the dispersion chamber 75, then fed to the conduit C1b from the discharge port 75b.

The above-mentioned operations are repeated while the discharge means (quantitative feeder) 71 is operated.

The lubricant L on the elastic membrane 73 is reduced by discharging lubricant L to the dispersion chamber 75 from the aperture (slit) 73s because of vibration of the elastic membrane 73 as shown in Fig.18(a) - Fig.18(c). When the amount of the lubricant L on the elastic membrane 73 is reduced from the height H, at which the level sensor 76 is provided, above the elastic membrane 73, the light receiving element 76b of the level sensor 76 receives light emitted from the light emitting element 76a.

In this embodiment the control means 111 opens the material feed valve 77 until the light receiving element 76b doesn't receive light emitted from the light emitting element 76a once it receives the light. Therefore, while the discharge means (quantitative feeder) 71 is operated, a fixed amount of lubricant L is always existed on the elastic membrane 73. There

is no phenomenon that the amount of lubricant L discharged in the dispersion chamber 75 from the aperture (slit) 73s of the elastic membrane 73 varies because of variation of the amount of lubricant L on the elastic membrane 73.

Further, vibration of the elastic membrane 73 as shown in Fig.18(a) - Fig.18(c) depends on the frequency, period, amplitude and wave shape of the pulsating vibration air supplied in the dispersion chamber 75. Therefore, if the pulsating vibration air is constant, a fixed amount of lubricant L can be always mixed with a fixed amount of air accurately.

When the pulsating vibration air is made constant, the amount of lubricant L mixed and dispersed in a fixed amount of air can be varied if the size (length) of the aperture (slit) 73s of the elastic membrane 73 is changed.

On the other hand, if the size (length) of the aperture (slit) 73s of the elastic membrane 73 isn't changed, at least one of the frequency, period, amplitude and wave shape of the pulsating vibration air is changed, then the amount of lubricant L mixed and dispersed in a fixed amount of air can be varied.

In this discharge means (quantitative feeder) 71 utilizes that the vibration of the elastic membrane 73 is determined according to the frequency, period, amplitude and wave shape of the pulsating vibration air. As a result, a fixed amount of lubricant L while dispersing in air can be always fed in the conduit C1b only by controlling the frequency, period, amplitude and wave shape of the pulsating vibration air.

Further according to the discharge means (quantitative feeder) 71, pulsating vibration air is made swirling flow directing from the introduction port 75a to the discharge port 75b in the dispersion chamber 75 as mentioned above, so that lubricant L fallen in the dispersion chamber 75 is suck in the swirling pulsating vibration air and fed to the conduit C1b after large lubricant powder L is broken into a desired particle diameter.

It is detailed hereinafter.

According to the discharge means (quantitative feeder) 71, pulsating vibration air is upwardly swirling from the introduction port 75a to the discharge port 75b as mentioned above, so that the dispersion chamber 75 has size classification function like a cyclone. Herewith, even if there is large particle in the lubricant L fallen in the dispersion chamber

75, such particle keeps swirling at the lower part of the chamber 75 so that it isn't fed out to the conduit C1b from the discharge port 75b.

Further while large particle keeps swirling at the lower part of the dispersion chamber 75, it is broken into a desired particle diameter by pulsating vibration air. The broken particle rides on upwardly swirling pulsating vibration air from the introduction port 75a to the discharge port 75b and is fed to the conduit (conduit C1b in Fig.13) connected to the discharge port 75b.

Therefore, when lubricant L is mixed and dispersed in pulsating vibration air by means of the discharge means (quantitative feeder) 71, a fixed amount of lubricant L having a fixed particle size is always supplied to the lubricant spraying means (lubricant spraying means 91 in Fig.13). As a result, lubricant L can be homogeneously applied on each upper punch 82 ···, lower punch 83 ···, and die 84 ··· without applying large particle of lubricant powder L.

Even if large particle is included in lubricant powder L supplied in the dispersion chamber 75, almost all of them is broken into a fixed particle size and is supplied to the lubricant spray means 91 so that large particle of lubricant L is hardly accumulated in the dispersing chamber 75.

Therefore, if such an external lubricant spraying type tabletting machine 51 is used for continuously compressing to produce tablet t, it isn't required for interrupting tabletting operation for cleaning the dispersion chamber 75 because of accumulated large particle of lubricant L therein while tabletting.

The numeral 78 in Fig.16 shows a remaining lubricant detection sensor for amount for detecting the remaining amount of lubricant L stored in the storage hopper 72. The detection sensor 78 has a light emitting element 78a for emitting visible light such as red light or light such as infra-red radiation and a light receiving element 78b for receiving the light emitted from the light emitting element 78a. The light emitting element 78a and the light receiving element 78b oppose at a fixed position above the material discharge port 72a of the storage hopper 72.

The remaining amount detection sensor 78 is connected to the control means (control means 111 in Fig.13) via a signal line (not shown).

The light emitting element 78a of the detection sensor 78 is always turned on while the discharge means (quantitative feeder) 71 is operated.

When adequate amount of lubricant L is stored in the storage hopper 72, the light emitted from the light emitting element 78a is blocked by the lubricant L so that the light receiving element 78b doesn't receive the light such as red light or infra-red radiation emitted from the light emitting element 78a.

On the other hand, the amount of lubricant L stored in the storage hopper 72 is reduced and the amount of the lubricant L becomes lower than the position where the light emitting element 78a and the light receiving element 78b are provided, the light emitted from the light emitting element 78a is received by the light receiving element 78b.

In this embodiment, at the time when the light receiving element 78b of the lubricant remaining amount detection sensor 78 receives the light emitted from the light emitting element 78a, a display means (not shown) of the control means 111 shows that the amount of the lubricant L in the storage hopper 72 is reduced in order to urge an operator to supply the lubricant L in the storage hopper 72.

The method for urging an operator to supply lubricant L in the storage hopper 72 isn't limited in displaying on the display means (not shown) of the control means 111. It goes without saying that an alarm lamp may be turned on or a warning buzzer may be sounded. In this embodiment only preferable embodiments are exemplified and the lubricant remaining amount detection sensor 78 isn't always necessary.

The numeral 79 in Fig.16 shows an observation means for viewing the condition of the lubricant L discharged in the cylindrical body 74 from the storage hopper 72.

The observation means 79 is connected to the control means (control means 111 in Fig.13) via a signal line (not shown).

The observation means 79 has an electronic flash 79a and an imaging means 79b such as solid-state imaging means like a liquid-crystal camera.

In this embodiment the control means 111 turns on the electronic flash 79a periodically or if required and the condition of lubricant L discharged in the cylindrical body 74 from the storage hopper 72 is taken by the imaging means 79b. The image information taken by the imaging means 79b is

temporally expanded and stored in an image memory of the control means 111 and is analyzed by an image analysis program stored in the memory means of the control means 111 in advance. When lubricant L isn't smoothly discharged in the cylindrical body 74 from the storage hopper 72, such information is displayed on the display means (not shown) of the control means 111 to inform an operator.

The observation means 79 having an electronic flash 79a and an imaging means 79b is explained above, however its only an exemplification. For example, an observation means which has a laser beam emitting means for emitting laser beam and a light receiving means for receiving scattering beam emitted by the laser beam emitting means and scattered by the particle of lubricant L falling in the cylindrical body 74 from the storage hopper 72 and wherein the condition of the lubricant L discharged in the cylindrical body 74 from the storage hopper 72 is observed based on the well-known Mie Scattering Theory. Further in this embodiment, only a preferable embodiment is exemplified and the observation means 79 isn't always required.

The numeral 80 in Fig.18 shows an observation means for viewing condition of the lubricant L in the dispersion chamber 75.

The observation means 80 is also connected to the control means (control means 111 in Fig.13) via a signal line (not shown).

This embodiment uses a probe type light scattering observation means incorporating an integrated combination of a laser beam emitting means for emitting laser beam and a light receiving means provided apart at a fixed distance from the laser beam emitting means.

When the probe type observation means 80 is inserted in the dispersion chamber 75, scattering light emitted from the laser beam emitting means and scattered by lubricant particle L passing between the laser beam emitting means and the receiving means is received in the light receiving means, the information received by the light receiving means is processed by a program based on a well-known Mie Scattering Theory stored in the control means 111 to analyze the condition of lubricant L in the dispersion chamber 75. In case of abnormality in the condition of lubricant L in the dispersion chamber 75, abnormality is shown on the display (not shown) of the control means 111 so as to call an operator's attention.

Next, construction and operation of the lubricant spraying means 91 used for the external lubricant spraying type tabletting machine 51 are explained in detail.

Fig.19 is a plane view diagrammatically showing the construction of a lubricant spraying means 91.

The lubricant spraying means 91 has a lower punch lubrication means 92 and an upper punch lubrication means 93. Both of them are fixedly provided at a fixed position above the rotary table 85 of the rotary type tabletting machine (rotary tabletting machine 81 in Fig.13).

The numeral 94 in Fig.19 is a fixing table for fixedly positioning the lubricant spraying means 91.

Fig.20 is an outer perspective view diagrammatically showing the upper punch lubrication means 93 of the lubricant spraying means 91 in Fig.19 when seen from the periphery of the rotary table 85 into the center thereof.

Fig.21 shows diagrammatic section along the line I-I in Fig.19. Fig.22 shows diagrammatic section along the line II-II in Fig.19.

In this embodiment, the upper punch lubrication means 93 is positioned forward (upper stream) of the rotational direction of the rotary table 85 against the lower punch lubrication means 92.

The rotary table 85 is rotated under the lubricant spraying means 91 in such a manner that its surface S85 is almost touched to a lower surface S92b of the lower punch lubrication means 92 of the lubricant spraying means 91 and a lower surface S93b of the upper punch lubrication means 93.

A guide groove g1 is formed on an upper surface S92a of the lower punch lubrication means 92 and comprises each passage of the upper punches 82 ··· along the rotary orbit of the upper punches 82 ··· in such a manner that each one of plural upper punches 82 ··· synchronously rotating with the rotary table 85 sequentially passes in the guide groove g1. When the position of the upper surface S92a of the lower punch lubrication means 92 is lower than the lower surface of each of the plural upper punches 82 ··· synchronously rotating with the rotary table 85, such a guide groove g1 isn't required.

The lower punch lubrication means 92 is provided in circumferential direction of the rotary table 85 so as to cover the plural dies 85 ··· from above, the dies being sequentially

fed under the lower punch lubrication means 92 by rotation of the rotary table 85.

The lower surface S92b of the lower punch lubrication means 92 is smoothly surfaced so as to smoothly slide the rotary table 85.

The numeral e1 in Fig.19 and Fig.21 shows a lubricant introduction pipe and the conduit (conduit C1b in Fig.13) is connected to the lubricant introduction pipe e1.

The lubricant (powder) L fed while dispersing in pulsating vibration air from the lubricant introduction port e1 to the lower punch lubrication means 92 via the conduit C1b is designed to be discharged from a discharge port e2 provided at the lower surface side S62b of the lower punch lubrication means 92 via a penetrating passage h1. The lubricant (powder) L fed while being dispersed in pulsating vibration air and discharged from the discharge port e2 is sequentially sprayed on each die 84 ··· fed under the lower punch lubrication means 92 and each lower punch 83 ··· inserted into a fixed position in each die 84 ···.

In more detail, the discharge port e2 vertically faces to the upper surface of the lower punch 83 inserted at a fixed position in the die 84 positioned under the lower punch lubrication means 92. Because of the aspect of the discharge port e2, the lubricant (powder) L fed while being dispersed in pulsating vibration air and discharged from the discharge port e2 of the lower punch lubrication means 92 is designed to be sprayed almost vertically on the upper surface of the lower punch 83 inserted in the die 84 fed below the lower punch lubrication means 92 by rotation of the table 85. Therefore, lubricant (powder) L is applied on the upper surface of the lower punch 83 and the upper part of the circumferential wall of the die 84 above the lower punch 83.

A long groove c1 is formed on the lower surface S92b of the lower punch lubrication means 92 into a direction of the upper punch lubrication means 93 from the position of the discharge port e2.

Lubricant (powder) L tends to be attached excessively on the upper surface S83 of the lower punch 83 under gravity.

However, even if extra lubricant (powder) is attached on the upper surface S83 of the lower punch 83, such an extra lubricant is blown out when pulsating vibration air blown together with lubricant L is at its peak so that extra lubricant

doesn't attach on the upper surface S83 of the lower punch 83.

Further, lubricant (powder) L blown from the upper surface S83 of the lower punch 83 is attached on the inner circumference S84 of the die 84 so that lubricant can be homogeneously attached on the inner circumference of the die 84 above the upper punch 83.

On the other hand, a long groove c2 is formed on the lower surface S93b of the upper punch lubrication means 93 along the rotary orbit of the plural dies 84 ··· provided for the rotary table 85.

The long groove c2 is connected with the long groove c1 provided on the lower surface S92b of the lower punch lubrication means 92.

An upper punch containing groove g2 is formed above the long groove c2 of the upper punch lubrication means 93 for sequentially containing each rotating upper punches 82 ···along the rotary orbit of the upper punch 82 ··· in such a manner that each one of plural upper punches 82 ··· rotating synchronously with the rotary table 85 sequentially passes in the groove g2.

Further, a slit 93s is provided at the center of the bottom of the upper punch containing groove g2 so as to penetrate therethrough along the rotary orbit of the upper punches 82 ···.

A suction head 95 is provided above the upper punch containing groove g2 and the conduit C2 connected to the suction means 101 in Fig.13 is connected to the suction head 95.

A suction port 95h of the suction head 95 is provided along the upper punch containing groove g2 from a tip end es to a terminal end ee.

According to the shape of the suction port 95h of the suction head 95, when the suction means (suction means 101 in Fig.13) is driven, air flow (negative flow) from the slit 93s to the suction port 95h is homogeneously generated between the tip end es to the terminal end ee of the slit 93s above the upper punch containing groove g2 of the upper punch lubrication means 93.

Air flow directing the long groove c2 of the upper punch lubrication means 93 from the lower punch lubrication means 92 is generated in a space between the long groove c1 formed on the lower surface S92b of the lower punch lubrication means 92 and the surface S85 of the rotary table 85.

Air flow (negative flow) homogeneously directing from the end of the long groove c1 to the slit 93s is generated between

the end of the long groove c1 and the end ee from the tip end es of the slit 93s in a space formed by the long groove c2 of the upper punch lubrication means 93 and the surface S85 of the rotary table 85.

Extra amount of lubricant (powder) L blown on the surface (inner circumference) of the die 84 fed under the lubricant spraying means 91, the surface (upper surface) of the lower punch 83 inserted in the die 84 together with pulsating vibration air is moved into the long groove c2 of the upper punch lubrication means 93 by an air flow (negative flow) generated by the suction means 103 from the lower punch lubrication means 92 to the long groove c2 of the upper punch lubrication means 93 in a space formed by the long groove c1 and the surface S85 of the rotary table 85 and by cooperation of this air flow (negative flow) and pulsating vibration air, then the lubricant is homogeneously moved to the suction port 95h from between the tip end es and the end ee of the slit 93s.

The air flow (negative flow) moving into the suction port 95h above the slit 93s is substantially laminar air flow in substance. In order to achieve this, a curb plate type current plate member may be provided on the slit 93s so as not to touch each surface (lower surface) of the upper punches 82 ··· which pass in the upper punch containing groove g2 of the upper punch lubrication means 93.

Lubricant (powder) L keeps colliding for a long time with the surface (lower surface) of each upper punch 82 ··· passing in the upper punch containing groove g2 of the upper punch lubrication means 93 under substantial laminar air flow (negative flow) while each upper punch 82 ··· moves from the tip end es to the end ee of the slit 93s. Therefore, lubricant (powder) L can be sequentially attached on the surface (lower surface) of each upper punch 82 ··· on which surface lubricant (powder) L is hardly attached because of gravity.

Extra amount of lubricant (powder) L supplied under substantial laminar air flow (negative flow) into the surface (lower surface) of each upper punch 82 ··· and lubricant (powder) L excessively attached on the surface of each upper punch 82 ··· are discharged in the suction port 95h by the substantial laminar air flow (negative flow). As a result, lubricant (powder) L is homogeneously applied on the surface (lower surface) of each upper punch 82 ··· in just proportion.

The numeral e3 in Fig.19 and Fig.21 shows a connection port for connecting the conduit (conduit C2 in Fig.13).

The numeral h2 in Fig.19 and Fig.21 shows a long suction port provided for the lower surface S92b of the lower punch lubrication means 92 so as to direct to the center from the periphery of the rotary table 85. The numeral e4 shows a connection port for connecting a conduit (not shown) connected to a suction means (not shown) to the suction port h2.

The suction port h2 is provided so as to remove extra lubricant (powder) L from the inner circumference S84 of the die 84 and the upper surface S83 of the lower punch 83 on which lubricant (powder) L is applied and to remove unnecessary lubricant (powder) L attached around the dies 84 of the rotary table 85 from the discharge port e2 of the lower punch lubrication means 92.

In this embodiment, the upper punch lubrication means 92 having a suction port h2 is explained, however, the suction port h2 isn't always necessary for the external lubricant spraying type tabletting machine 51.

Next, process of applying lubricant (powder) L on the surface (lower surface) of each upper punch 82 ···, the surface (upper surface) of each lower punch 83 ···, and the surface (inner circumference) of each die 84 ··· is explained hereinafter.

The control means 111 is turned on.

A main power of the rotary type tabletting machine 81 is turned on and a main power of the pulsating vibration air generation means 61 is also turned on.

Depending on the physical property and chemical nature of used lubricant (powder), the rotary cam 67 having suitable concavo-convex patterns p1, p2 for generating pulsating vibration air in which lubricant (powder) is easily mixed and dispersed is attached on the rotary axis 65a of the drive means 65 of the pulsating vibration air conversion means 63 of the pulsating vibration air generation means 61.

The granulated material produced as mentioned above is contained as molding material in the molding material storage hopper (not shown) of the molding material charge means (feed chute) 121.

Lubricant (powder) L is contained in the storage hopper 72 of the discharge means (quantitative feeder) 71.

The level sensor 76 of the discharge means (quantitative

feeder) is turned on so as to make the material feed valve 75 on active condition.

When the level sensor 76 is turned on, the material feed valve 75 is opened so that lubricant (powder) L is discharged in the cylindrical body 74 from the storage hopper 72.

When the amount of the lubricant (powder) L in the cylindrical body 74 becomes at the height H above the elastic membrane 73 of the cylindrical body 74 of the discharge means (quantitative feeder) 71, the material feed valve 75 is closed and discharge of lubricant (powder) L in the cylindrical body 74 from the storage hopper 72 is stopped.

Then the suction means 101 and the rotary type tabletting machine 81 are driven.

Accordingly plural upper punches 82 ···, lower punches 83 ···, and the rotary table 85 of the rotary type tabletting machine 81 are synchronously rotated at a fixed speed.

Also the air source 62 of the pulsating vibration air generation means 61 and the drive means 65 are driven so as to rotate the rotary cam 67 at a fixed speed.

If the flow rate control means 64 is provided, it may be properly adjusted.

If the output control valve v is provided, it may be properly adjusted.

The drive means 65 is driven and the rotary cam 67 is controlled so as to rotate at a fixed speed by means of the control means 111.

The drive amount of the air source 62 is also controlled if required.

As mentioned above, desired pulsating vibration air is fed in the conduit C1b.

The pulsating vibration air fed in the conduit C1b then enters in the dispersion chamber 75 from the introduction port 75a and becomes swirling flow toward the discharge port 75b from the introduction port 75a therein.

Herewith, the elastic membrane 73 is vibrated according to the period, frequency, amplitude and wave shape of pulsating vibration air, the aperture (slit) 73s of the elastic membrane 73 is opened and closed, then the lubricant (powder) L on the elastic membrane 73 in the cylindrical body 74 is dropped.

The lubricant (powder) L thus fallen in the dispersion chamber 75 is suck in swirling pulsating vibration air and mixed

and dispersed therein.

The lubricant (powder) L thus mixed and dispersed in the pulsating vibration air is fed to the conduit C1b from the discharge port 75b of the dispersion chamber 75.

The pulsating vibration air fed in the conduit C1b is supplied in the lower punch lubrication means 92 from the lubricant introduction port e1.

The lubricant (powder) L thus fed in the lower punch lubrication means 92 from the lubricant introduction port e1 is sprayed on the die 84 fed under the lubricant spraying means 91 according to rotation of the rotary table 85 and the lower punch 83 inserted at a fixed position of the die 84 from the discharge port e2 of the lower punch lubrication means 92 together with pulsating vibration air.

Extra amount of lubricant (powder) L sprayed on the die 84 fed under the lubricant spraying means 91 and the lower punch 83 inserted at a fixed position of the die 84 together with pulsating vibration air moves in the long groove c2 of the upper punch lubrication means 93 and homogeneously moves into the suction port 95h from between the tip es and the end ee of the slit 93s by air flow (negative flow) directing the long groove c2 of the upper punch lubrication means 93 from the lower punch lubrication means 92 in the space formed by the long groove c1 and the surface S85 of the rotary table 85 and by cooperation of this air flow (negative flow) and pulsating vibration air when the suction means (suction means 101 in Fig.13) is driven.

Lubricant (powder) L keeps colliding for a long time with the surface (lower surface) of each upper punch 82 ··· passing in the upper punch containing groove g2 of the upper punch lubrication means 93 under substantial laminar air flow (negative flow) while each upper punch 82 ··· moves from the tip end es to the end ee of the slit 93s. Therefore, lubricant (powder) L can be sequentially attached on the surface (lower surface) of each upper punch 82 ··· on which surface lubricant (powder) L is hardly attached because of gravity.

Extra amount of lubricant (powder) L supplied under substantial laminar air flow (negative flow) into the surface (lower surface) of each upper punch 82 ··· and lubricant (powder) L excessively attached on the surface of each upper punch 82 ··· are discharged in the suction port 95h by the substantial laminar air flow (negative flow). As a result, lubricant (powder) L

is homogeneously applied on the surface (lower surface) of each upper punch 82 ··· in just proportion.

Granulated material stored in the storage hopper (not shown) is sequentially charged in the space formed by each die 84 ··· on which surface (inner circumference) lubricant (powder) L is homogeneously sprayed and each lower punch 83 ··· on which surface (upper surface) lubricant (powder) L is homogeneously sprayed and which is inserted in each die 84 ··· into a fixed position from the molding material charge means (feed chute) 121.

Next extra amount of molding material m supplied in the space formed by the die 84 and the lower punch 83 inserted in the die 84 is scraped and removed by the scraper 122 provided at the end of the molding material charge means (feed chute) 121.

According to the above-mentioned processes, molding material m supplied in the space formed by the surface (inner circumference) of the die 84 and the surface (upper surface) of the lower punch 83 which is inserted in a fixed position in the die 84 is pre-compressed by the upper punch 82 on which surface (lower surface) lubricant (powder) L is homogeneously applied and the lower punch 83 on which surface (upper surface) lubricant (powder) L is homogeneously applied. Then the material m is further compressed at the actual compression point P4 to be a tablet t. Thus produced tablet t is discharged at a fixed place by the tablet discharge arm 131 at the tablet discharge position P5.

In this embodiment each one of plural upper punches 82 ···, each one of plural lower punches 83 ···, each one of plural dies 84 ··· are fed to the cleaning position P6 after the tablet t is discharged at the tablet take out position P5. Remaining lubricant (powder) L and/or molding material m (granulated material in this embodiment) are completely removed by each of upper punch cleaning means (not shown), lower punch cleaning means (not shown), and die cleaning means (not shown) provided at the cleaning position P6 for preparing next tabletting procedure.

According to the external lubricant spraying type tabletting machine 51, lubricant (powder) L mixed and dispersed in pulsating vibration air is sprayed in a short time on each surface (upper surface) of the lower punches 83 ··· on which extra lubricant is easily attached because of gravity. Further,

lubricant (powder) L is also applied on each surface (inner circumference) of the die 84 ··· at a short time by pulsating vibration air. Further lubricant is homogeneously attached on the surface (upper surface) of the lower punch 83 ··· and the surface (circumferential wall) of the dir 84 ···by sucking and removing extra lubricant (powder) L.

Lubricant (powder) L is applied on each surface (lower surface) of the upper punch 82 ···, on which lubricant has difficulty in attaching, in a different way from the method of applying lubricant on the surface (upper surface) of the lower punch 83 ··· and the surface (inner circumference) of the die 84 ···. Namely, lubricant (powder) L is homogeneously attached on each surface (lower surface) of the upper punch 82 ··· passing in the upper punch containing groove g2 under substantial laminar air flow (negative flow) for a long time while the upper punch 82 ··· moves from the tip es to the end ee of the slit 93s in the upper punch lubrication means 93.

According to the external lubricant spraying type tabletting machine 51, lubricant (powder) L is applied on each surface (upper surface) of the lower punch 83 ··· and each surface (inner circumference) of the die 84 ··· under positive pressure such that positive pulsating vibration air mixed with lubricant (powder) L is sprayed, under turbulent airflow and at a short time. On the other hand, lubricant (powder) L is applied on each surface (lower surface) of upper punch 82 ··· under negative pressure, under substantial laminar air flow and at a long time. Thus lubricant (powder) L is applied on each surface (upper surface) of the lower punch 83 ···, each surface (inner circumference) of the die 84 ···, and each surface (lower surface) of upper punch 82 ··· by suitable methods.

Thus, lubricant (powder) L can be homogeneously applied on each surface (lower surface) of upper punch 82 ···, each surface (upper surface) of the lower punch 83 ···, and each surface (inner circumference) of the die 84 ···. Therefore, when tablet without including lubricant is tabletted, grinding isn't caused for the upper punch 82 ···, the lower punch 83 ···, and the die 84 ··· and molding material m (granulated material in this embodiment) doesn't attach on them so that tabletting problems such as sticking aren't happened for the produced tablet t.

The tablet without including lubricant therein as shown in this embodiment can be produced by the several methods shown

in the prior art of the present specification. However, when such an external lubricant spraying type tabletting machine 51 is used, lubricant can be homogeneously applied on each surface (upper surface) of the lower punch 83 ···, each surface (inner circumference) of the die 84 ···, and each surface (lower surface) of the upper punch 82 ··· comparing with those prior methods so that the tablet of the present invention can be produced at high productive efficiency.

Further according to the external lubricant spaying type tabletting machine 51, the light scattering type powder density measuring means 112 is provided for the conduit C2 for measuring the density of the lubricant (powder) L flowing in the conduit C2. Therefore, the density of the lubricant (powder) L sprayed from the lubricant spraying means 91 can be controlled also by adjusting driving amount of the suction means 101 based on the detected value of the light scattering type powder density measuring means 112.

Still further according to the external lubricant spaying type tabletting machine 51, the lower punch lubrication means 92 of the lubricant spraying means 91 has the long suction port h2 provided on the lower surface S92b of the lower punch lubrication means 92 so as to direct from the periphery to the center of the rotary table 85.

If such a lubricant spraying means 91 having the suction port h2 is used, trial tabletting is executed before executing full tabletting, then the produced sample tablet is pulverized and the amount of lubricant L contained in one tablet is measured. If the amount of lubricant L contained in one tablet is larger than the predetermined amount, a part of lubricant (powder) L attached on each surface (inner circumference) of the die 84 ··· is suck and removed or a part of lubricant (powder) L attached on each surface (upper surface) of the lower punch 83 ··· is suck and removed by driving the suction means (not shown) connected to the suction port h2 at a proper driving amount.

If lubricant (powder) L is attached around each die 84 ··· of the rotary table 85 or there is such a fear, an operator may operate the suction means (not shown) connected to the suction port h2 at appropriate time or full-time at proper driving amount so as to clean around each die 84 ··· of the rotary table 85. When the suction means (not shown) connected to the suction port h2 is operated in such a manner, tablet without including

lubricant can be produced so that intrabuccally rapidly disintegrable tablet which is more rapidly dissolved in oral cavity can be produced.

Although the same intrabuccally rapidly disintegrable tablet, disintegration time in oral cavity can be differed by changing combination ratio of saccharide with high wettability against water included in binder so that the present invention has an effect of controlling disintegration time in oral cavity.

Industrial Applicability

As explained above, according to the tablet of claim 1, a saccharide with high wettability against water is used and the particle of granulated material is bound by a binder including a saccharide with high wettability against water. According to this construction, when the tablet is given in oral cavity, the saccharide with high wettability against water in binder rapidly gets wet by saliva and dissolved or dispersed therein. Therefore, the binding force of the binder particle becomes weak and the granulated material is dissolved so that the tablet is rapidly dissolved.

On the other hand, as the particle comprising tablet is bound by a binder and the binding force is strong, the tablet doesn't get chipped while storage and transportation.

Further according to such a tablet, functional coating (for example enteric coating) is executed for granule including a principal agent in such a manner that the principal agent is dissolved at an objected part, sustained release coating is executed so that the tablet is dissolved gradually, a solid dispersing granule is prepared so as not to crystallize the principal agent, or a principal agent is made granule dispersed in a wax matrix construction so that rapid disintegrable medicine in oral cavity can be achieved.

The tablet described in claim 2 further includes the saccharide particle with high moldability in the granulated material so that such tablet is more excellent in moldability in addition to the effect of the tablet described in claim 1.

According to the tablet described in claim 3, the blend ratio of the particle of wettable saccharide and the particle of saccharide with high moldability is set in such a manner that the tablet which is excellent in moldability of compression and is rapidly disintegrated in oral cavity can be produced.

Therefore, the tablet rapidly disintegrable in oral cavity can be produced at high productivity.

According to the tablet described in claim 4, a saccharide which is excellent in safety and moldability and is available is selected as a saccharide with high moldability so that a tablet with high safety, moldability and rapid disintegrability in oral cavity can be easily produced

According to the tablet described in claim 5, a saccharide which is excellent in safety and wettability and is easily available is selected as a saccharide with high wettability against water, so that a tablet which has excellent safety and is rapidly disintegrated in oral cavity can be easily produced.

Further, because the viscosity of the solution of the saccharide with high wettability against water isn't increased when being dissolved in water, water in saliva is easily permeated in the tablet. The tablet is rapidly dissolved by saliva in oral cavity because of such function.

According to the tablet described in claim 6, the particles are bound by a binder including a surface active agent other than a saccharide with high wettability against water.

Therefore, the binder becomes easily wettable because the boundary tension of water in saliva is lowered by a surface active agent in the binder when the tablet is in oral cavity. Then the saccharide with high wettability against water is quickly wetted and dissolved or dispersed in saliva from the binder. Accordingly the binding force of binder is lost and granulated material is dissolved rapidly.

According to the tablet described in claim 7, the particle of granulated material is bound by a water-soluble polymer including a saccharide with high wettability against water. Therefore, a binder is permeated in water in saliva when it contacts saliva in oral cavity. As a result, because the granulated material is quickly disintegrated and dispersed into particle level, the tablet can be rapidly disintegrated in oral cavity.

Further according to the tablet, the particle of saccharide with high wettability against water is dispersed in a water-soluble polymer binding between the particles comprising the granulated material. According to such a tablet, the particle of saccharide with high wettability against water dispersed in a water-soluble polymer is dissolved into saliva

when it contacts saliva in oral cavity. According to such construction, when the tablet is in oral cavity, a saccharide with high wettability against water in a binder quickly gets wet by saliva therein and dissolved or dispersed in saliva. As a result, the binding force of the particle in a binder becomes weak so that such tablet is rapidly disintegrated comparing with the tablet in which particle comprising granule is bound only by a water-soluble polymer.

According to the tablet production method described in claim 8, an intrabuccally rapidly disintegrable tablet can be produced by means of a fluid bed granulation method and a compression mold method used for producing a normal tablet so that a new and particular apparatus isn't required for producing an intrabuccally rapidly disintegrable tablet.

According to the tablet produced by such a production method, a granulated material included therein is bound by a binder including a saccharide with high wettability against water. Therefore, it is superior in disintegrability in oral cavity comparing with the tablet in which a granulated material using only a binder is compressed.

Also according to the tablet production method described in claim 9, an intrabuccally rapidly disintegrable tablet can be produced by means of a fluid bed granulation method and a compression mold method used for producing a normal tablet so that a new and particular apparatus isn't required for producing an intrabuccally rapidly disintegrable tablet.

In the tablet produced by such a production method, the particle comprising a granulated material included in tablet is bound by a binder including a saccharide with high wettability against water. Therefore, it is superior in disintegrability in oral cavity comparing with the tablet in which a granulated material using a binder including only a water-soluble polymer is compressed.

Further according to this production method, the particle of saccharide with high moldability is included in the granulated material. Thereby, tabletting problems such as sticking aren't caused for the produced tablet.

According to the tablet production method described in claim 10, a surface active agent is added in a binder. Therefore, in the tablet produced by this method, the particle comprising a granulated material included in the tablet is bound by a binder

including a surface active agent other than a saccharide with high wettability against water so that such a tablet is more rapidly disintegrated in oral cavity.

According to the tablet production method described in claim 11, a water-soluble polymer is used as a binder and a binder is permeated in water in saliva when the tablet produced by this production method touches saliva in oral cavity. Therefore, the granulated material is quickly dissolved and dispersed into particle level and rapidly disintegrated in oral cavity.

Further according to such a tablet, the particle of saccharide with high wettability against water is dispersed in a water-soluble polymer binding between the particles comprising the granulated material. Therefore, when such a tablet produced by this production method touches saliva in oral cavity, the particle of saccharide with high wettability against water dispersed in a water- soluble polymer is dissolved in saliva. According to such construction, when the tablet is given in oral cavity, a saccharide with high wettability against water in a binder quickly gets wet and dissolved or dispersed in saliva. Therefore, the binding force of the particle in the binder becomes weak and the granulated material is disintegrated so that the table is rapidly disintegrated.

According to the tablet production method described in claim 12, the ratio of the binder and the saccharide with high wettability against water included in the aqueous solution used for the granulation is adjusted in such a manner that the compressed tablet has practical hardness and the tablet is rapidly dissolved in oral cavity. Therefore, an intrabuccally rapidly disintegrable tablet which is hardly chipped during storage and transportation and is rapidly dissolved in oral cavity can be produced.